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ORIGINAL ARTICLES

ANGIOCARDIOGRAPHIC STUDIES ON THE HUMAN FOETAL CIRCULATION

A Preliminary Report

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ANGIOCARDIOGRAPHIC investigations on the circulation in the foetal lamb before and after delivery were presented by Barclay, Franklin and Prichard in a monograph published in 1945.[1] These authors presented new observations with conclusions of great importance for cardiologic investigation. They stressed, however, the difficulty of transferring the findings established in animal experiments to the human foetal circulation and the desirability of further angiocardiographic studies on human foetuses.

The present preliminary report proposes to show that it is possible to carry out angiocardiography on human foetuses. The investigations have been carried out in connection with legal abortions, in which the age of the foetus has ranged from 18 to 22 weeks; the studies have been facilitated by the assistance of the Gynecological Department II and the Surgical Department at the Sabbatsberg Hospital, Stockholm.

The roentgenographic technic used is direct photography on full-sized cassettes with an exposure time and correspondent exchange of cassettes of 10 pictures per second.

This apparatus was built originally by the authors in collaboration with the Schönander X-Ray Company for angiocardiography on children and is described in detail by Fredzell, Wasser and Wegelius.[2] This report is restricted to the main features of its construction and the mode of operation of the apparatus.

METHOD

A magazine for 60 roentgen film cassettes is placed directly beneath the exposure field. In the bottom of each cassette there is a lead sheet, so that only the uppermost cassette is exposed. An eccentric arm driven by a synchronous motor strikes the uppermost cassette from the side once per

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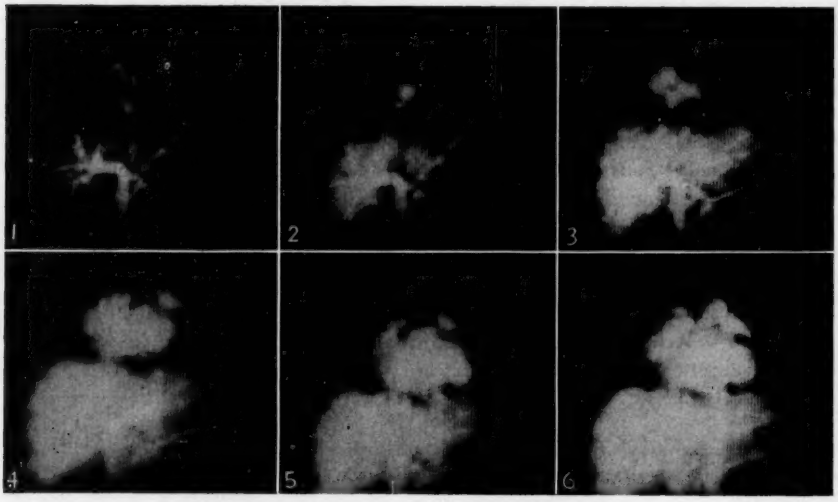
PLATES I and II—Case A. Autopsy

Plate I. Interior thoracic wall is removed and lungs pulled aside to expose heart and great vessels. Superior vena cava with its branches are seen as well as aortic arch, great arteries and main branches of left pulmonary artery.

Plate II. Superior vena cava and aortic arch with ductus arteriosus are seen in oblique view. Left auricular appendix is large and fringed.



FIGS. 1-6—Case A. Foetus aged approximately 20 wks.

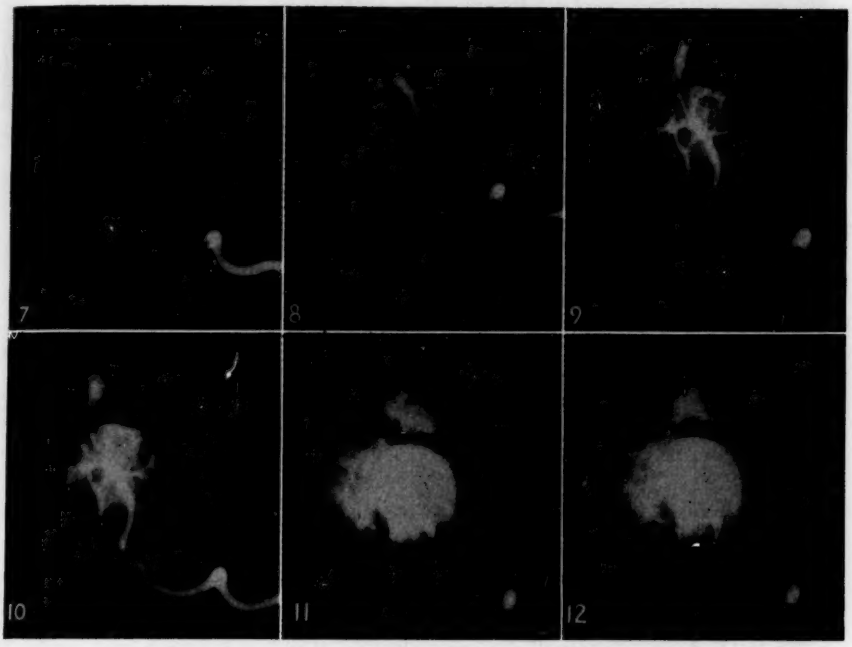
Fig. 1 (Film 34). Hepatic vascular system, auricles and right auricular appendix.

Fig. 2 (Film 35). Reflux of contrast into superior vena cava. Beginning filling of ventricles.

Fig. 3 (Film 36). Increased filling of cavities of heart.

Fig. 4 (Film 40). Superior vena cava with its branches and aorta appear distinctly. Both intense

revolution. The exposures are released by a micro-switch in the cam of the motor during that period in which the eccentric arm is not in the field of exposure. By means of helical springs attached to the back of the magazine, unexposed cassettes are pressed forward to exposure position in the place of those ejected. By this procedure, the side displacement of the cassettes is reduced to 1 phase



FIGS. 7-12—Case B. Foetus aged approximately 19 wks.

Fig. 7 (Film 11). Contrast medium passing in through umbilical vein.

Fig. 8 (Film 12). Contrast filling of vascular network of liver, ductus venosus and auricle.

Fig. 9 (Film 13). Inferior vena cava and hepatic veins distinct.

Fig. 10 (Film 14). Filling of right auricular appendix and ventricles.

Fig. 11 (Film 24). Good contrast filling of heart and beginning filling of aorta ascendens and arcus. Ventricles in diastole.

Fig. 12 (Film 26). Aorta descendens is now also visualized, well filled. Ventricles in systole. Pulmonary cone and ductus arteriosus now appear distinct.

instead of the more time-consuming and technically more difficult dual phase required by the sideways feeding in and ejection of the cassettes. Exposure time is determined on the basis of the periods of the alternating current, this being fixed at exactly 1 period of the supply frequency, the beginning of which, after the closure of the micro-switch of the motor, determines its release, while its termination is an automatic sequence of the termination of the period. In the alternating current prevalent in this country with 50 periods/sec., this implies that every 5th period is used for the present exposure time of 0.1 sec. By this procedure the exposure time is obviously permanently fixed at 0.02 sec., while kilovoltage and amperage may be varied arbitrarily as required.

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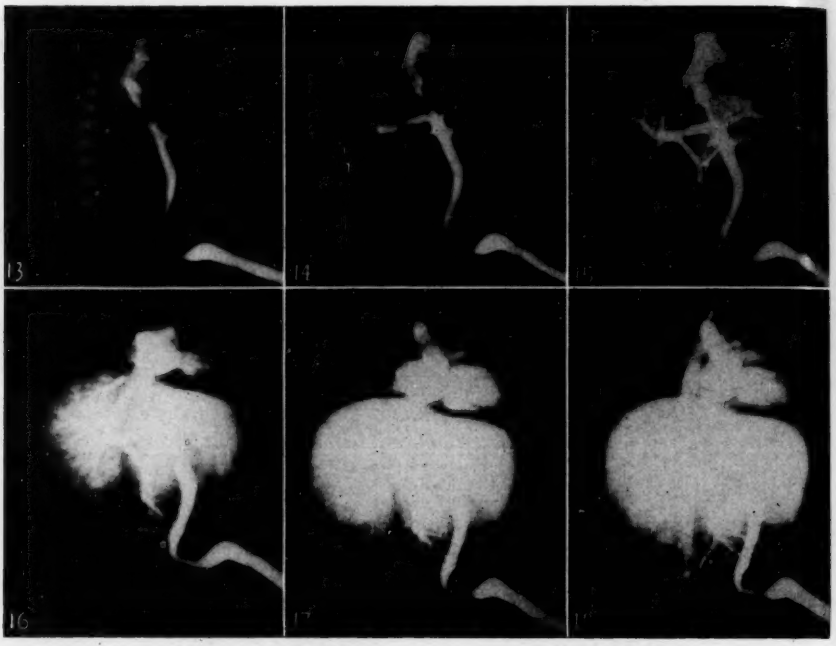
rounded spot as well as triangular shadow under arcus and partly superimposed on aorta descendens correspond to large dilatated left auricular appendix.

Fig. 5 (Film 46). Density is decreased in left auricular appendix now emptied. Ductus arteriosus appears.

Fig. 6 (Film 64). Aorta is visualized in its entire length. Auricular appendix is again more rounded and contrast-filled.



FIGS. 13-18—Case C. Foetus aged approximately 22 wks.

Fig. 13 (Film 2). Direct flow of contrast into auricles via ductus venosus. Coincident beginning contrast filling of hepatic circulatory system.

Fig. 14 (Film 3). Increased density of hepatic vascular tree and auricles.

Fig. 15 (Film 4). Filling of auricular appendix and beginning flow of medium into ventricles.

Fig. 16 (Film 8). Hepatic circulatory system filled in toto; hepatic veins converging towards inferior vena cava also stand out distinctly. Ventricles are filled.

Fig. 17 (Film 18). Auricles and ventricles are well opacified as is aorta with its large arterial trunks departing from arcus; ventricles in diastole.

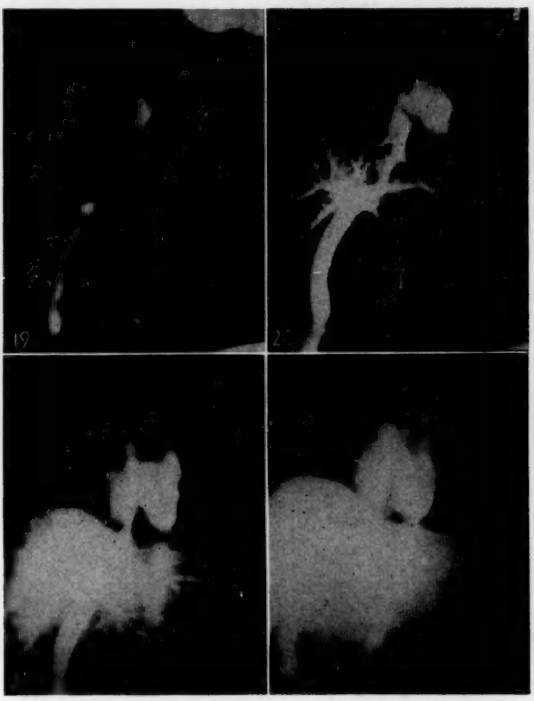
Fig. 18 (Film 32). Ventricles in systole, increased opacity in aorta. Pulmonary trunk and ductus arteriosus all appear closely.

In sharp contrast to intensity of hepatic circulatory system as well as of heart and aorta, vascular tree of lungs shows no contrast filling.

DISCUSSION

There are certain principal differences between this technical method and those used by Barclay, Franklin and Prichard as well as other roentgenographic procedures in angiocardiography described in the literature. The central feature of the method is the solution of the problem: rapid exchange of cassettes with separate exposures in direct roentgenography. An increase of the rate of exposure beyond approximately two pictures per second has to date been practicable only in the so-called cinematographic fluorography, i.e., photography on substandard film of the image on the fluorescent screen. The authors previously mentioned, however, as well as other workers in angiocardiography, stress the superior quality of the direct full-sized photography as compared with fluorography. There is not only the question of the advantages of a conveniently interpretable primary

material in the form of full-sized roentgen film, which does not require the projective enlargement of the fluorographic film, but also of the better reproduction of details of the directly photographed picture with its superiority in both contrast and clarity. This factor is obviously of greater importance the smaller the object, with corresponding difficulties in differentiating the proportionally far smaller individual details. In angiocardiography of the present series of human foetuses in ages 18 to 22 weeks where, by



FIGS. 19-22—Case D. Foetus aged approximately 18 wks.

Fig 19 (Film 22). Beginning and as yet scanty filling of hepatic circulatory system. Coincident direct passage through ductus venosus and auricles into aorta via left ventricle.

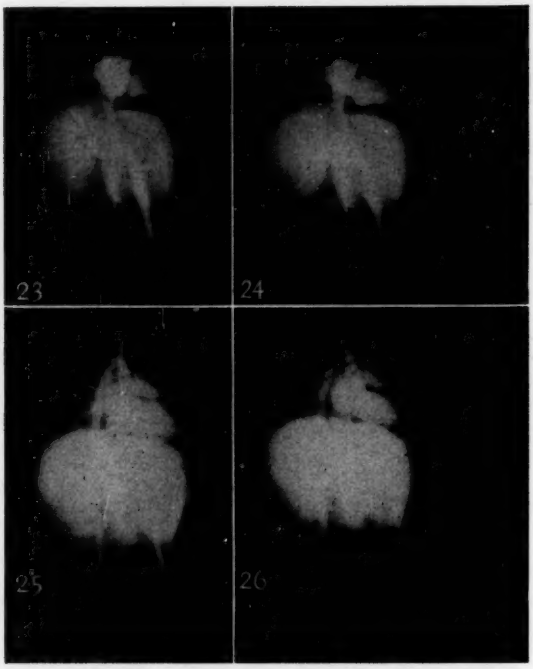
Fig. 20 (Film 26). Finely distributed network of hepatic circulatory system appears distinctly. Increasing density of heart and aorta.

Fig. 21 (Film 36). Auricles, ventricles and aorta markedly contrast filled. Ventricles in systole.

Fig. 22 (Film 48). Ductus arteriosus and pulmonary artery now stand out distinctly. Negligible contrast filling of lungs. Ventricles in diastole.

way of example, the great efferent vessels, aorta, pulmonary artery and ductus arteriosus have a calibre of 1 mm. and lie closely adjacent to each other, the need of a meticulous reproduction of detail is naturally many times greater than in correspondent photography of these vessels in the adult in whom these vessels have a calibre up to 20 to 30 times greater. The direct roentgenography with its qualitative superiority was thus the method of choice in this study. A second demand was an exposure sequence sufficiently rapid for a continuous following of the dynamic processes with regard to the direction and rate of

flow of the blood stream as well as to the morphologic changes of the heart and its relationships to the great vessels during various phases of the cardiac cycle. In these respects the rate of exposure of 10 pictures per second obtained in the present investigations seems to afford comparatively good results. Moreover, photography on serial film of a sequence of up to 60 pictures during 6 seconds permits an acceptable cinamatographic visualization of the course of the angiocardiography. The method presented thus combines



FIGS. 23-26—Case E. Foetus aged approximately 20 wks.

Fig. 23 (Film 3). Abundant contrast filling of hepatic circulatory system as well as of auricles, ventricles and pulmonary trunk; slight opacification of aorta. Auricles in diastole, ventricles in systole.

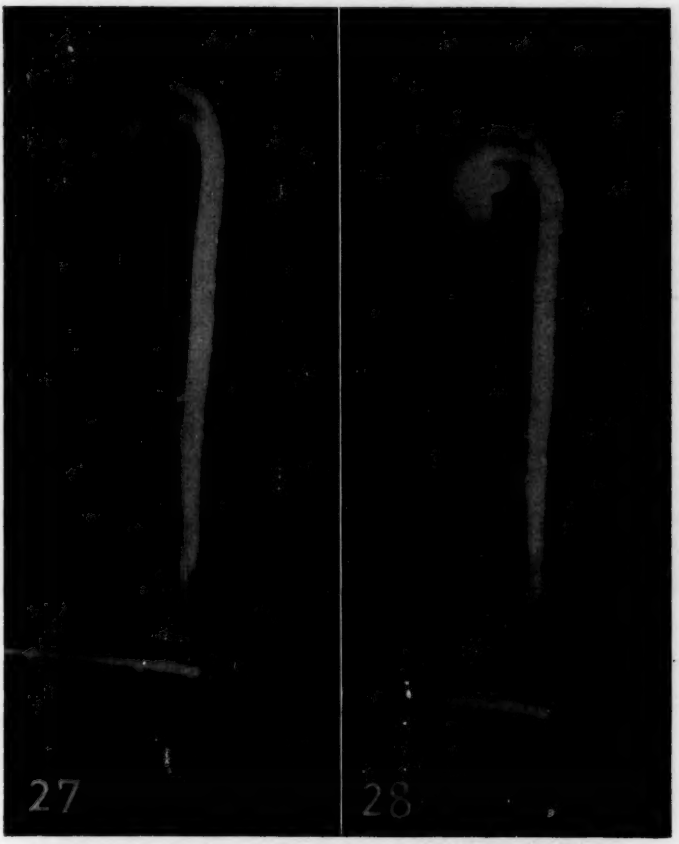
Fig. 24 (Film 4). Aorta and one of main branches of pulmonary artery now appear more distinctly. Auricles empty into larger ventricles during diastole, thereby decreasing in volume.

Fig. 25 (Film 18). Intensive contrast filling of all cavities of heart. Aorta and ductus arteriosus appear distinctly. Auricular appendix well filled. Observe coarse calibre of cephalic arteries as compared with fine calibre of arteries of pelvis and lower extremities. (Contrast is passing out through umbilical arteries.)

Fig. 26 (Film 33). Three great main trunks, aorta, ductus arteriosus and pulmonary artery, stand out especially distinctly.

the "slow" detailed direct photography and the "rapid" indirect photography, less detailed although serviceable for dynamic angiocardiographic studies, a combination which Barclay and others considered incompatible.

In the present investigations, the following technical data were applied with the apparatus previously described: Focal distance 100 cm. Kilovoltage 70 to 75 KV. Current 250 to 300 mA. A cone-tube adjusted to the focal spot served as a primary diaphragm



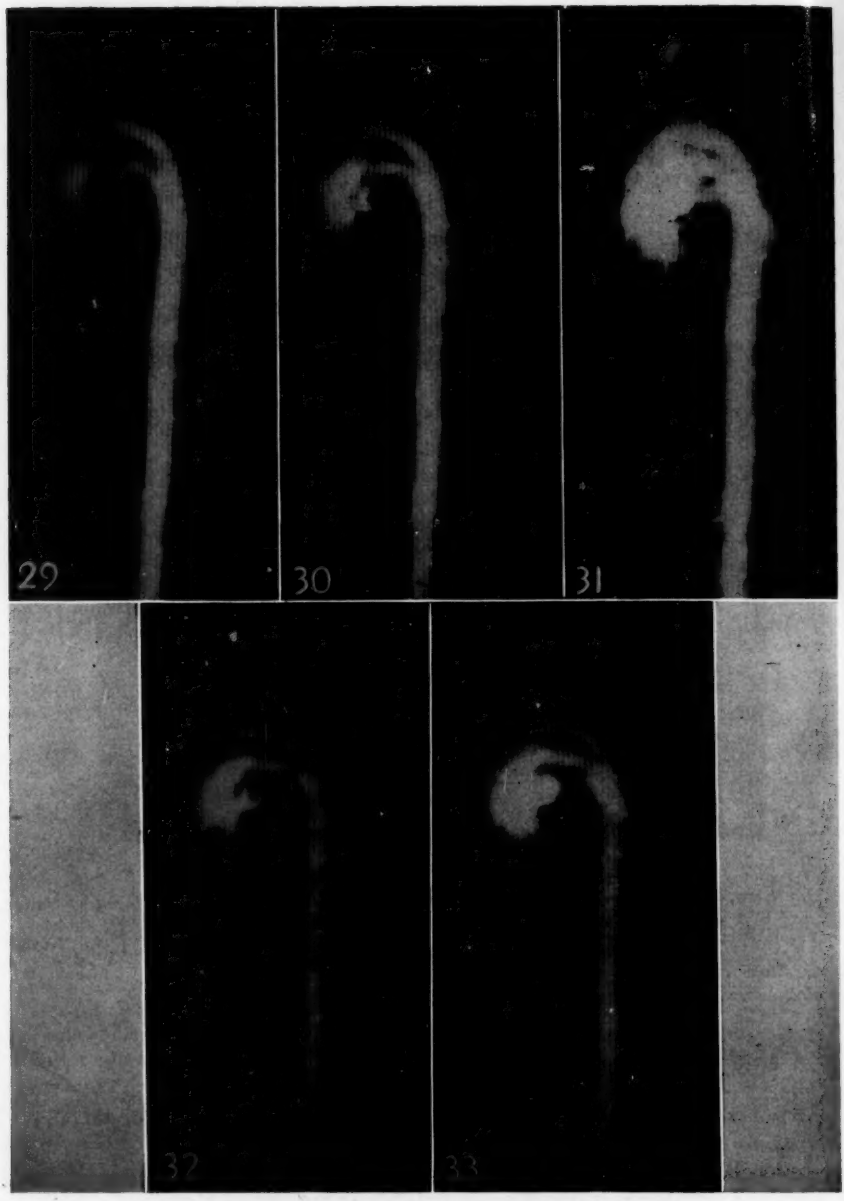
FIGS. 27-34—Case F. Foetus aged approximately 19 wks.

Fig. 27 (Film 2). Injection needle in one of umbilical arteries. Intensive contrast filling of aorta, ductus arteriosus and great arteries departing from arch of aorta, and also of mesenteric artery.

Fig. 28. (Film 5). In addition to visualization in Fig. 27, pulmonary artery and its branches now appear filled. Aortic and pulmonic valves tight, absence of retrograde leakage, valves outlined. Beginning diffuse filling of heart wall via well filled coronary vascular branches.

and a standard one-way Lysholm grid as a secondary diaphragm. Exposure rate 10 pictures per second with fixed intervals of 0.98 sec. Exposure time 0.02 sec. The details are conspicuously distinct, evidently owing to the short exposure time, with no appreciable blurring due either to cardiac dynamics, blood flow or the not inconsiderable foetal movements being traceable.

The angiocardiography is carried out immediately on the removal of the foetus in intact membranes by cesarian section under ether anesthesia. The membranes were incised on the angiocardiography table placed beside the operating table and injection of the contrast medium made through the vessels of the umbilical cord. As a rule, the injection was carried out within one half to one minute after cutting the membranes. An electric



FIGS. 29-33. Specific details in enlargement of successive Films 2-6 (at intervals 0.1 sec. after injection): Successive fillings of vessels appears clearly. Uppermost of contrast filled arches is arch of aorta; below it is ductus arteriosus and nethermost is pulmonary artery, which is not clearly visualized until Fig. 28 where contrast has passed circuit aorta—ductus arteriosus—pulmonary conus and pulmonary trunk.

radiator was placed immediately above the foetus. The contrast medium used was 70% Umbradil (Astra). The exposures were generally carried out in the left oblique position, in some instances also in the right oblique, and with slow rotation of the foetus for the attainment of different projections.

In regard to the findings obtained the reader is referred to the illustrations and their

FIG. 34. Specific details in enlargement of successive exposure Film 15 (1.5 sec. after injection). Marked diffuse contrast filling of heart muscle. Note contrast visualization of thyroid gland.

legends (see Figs. 1-34 and Plates I and II). The film number shown after each figure number in the legends indicates that with the present exposure time of 10 pictures per second the time interval between the consecutively numbered pictures is 0.1 sec.; e.g., in Figures 3 and 4 (Films 36 and 40) there is an interval of 0.4 sec.

In a number of cases the findings were verified by autopsy, a solidifying contrast medium being injected through the vessels of the umbilical cord. The roentgenography was then carried out with the subject in a position correspondent to that in the angiocardiography. At autopsy the angiocardiography films were compared with these radiograms and with the anatomic findings.

Although no specified conclusions belong in a preliminary report such as this, the picture series presented nevertheless may justify some general conclusions.

Angiocardiography of the human foetus according to the method reported is technically feasible and permits a roentgen-diagnostically acceptable picture quality. The hepatic circulatory system, ductus venosus, the cardiac chambers and the great vessels are visualized with a clarity which allows an entirely satisfactory differentiation.

The contractions of the heart continue until after the heart and the great vessels have been filled with the contrast medium with an intensity which clearly delineates the cavities and the lumina of the vessels.

The exposures seem to be sufficiently rapid to permit both an assessment of the circulatory dynamics and the course of the blood stream. The rapid flow of the blood stream into the heart via the ductus venosus has been demonstrated and also its further course directly via the left ventricle to the arterial circulation. Direct determinations of the rate of circulation are possible by the interval for the return of the contrast medium to the arteries of the umbilical cord extraneous to the foetus. The capacities of the cardiac chambers are visualized in the various phases of the cardiac cycle and also the different stages of filling of the efferent vessels in relation to the contractions of the heart.

The foetal pulmonary circulatory system shows only slight filling with the opaque contrast medium, an expression of its assumed partial segregation from the general circulation during foetal life.

It seems feasible to determine in vivo the calibre of the greater vessels of both the venous and the arterial circulation in various regions. In addition to comparisons between the ductus venosus and the hepatic veins, and between the ductus arteriosus and pulmonary artery and aorta, the difference between the markedly larger calibres of the arteries of the upper as compared to those of the lower half of the body is striking. This latter finding is in agreement with the earlier anatomic observations.

SUMMARY

Direct radiographic angiocardiography with 10 exposures per second on human foetuses in legal abortions is described. The technical solution combines the advantages of a high picture quality with a possibility of assessing the dynamic course in the heart and the circulation in both the arterial and the venous circulatory system. The foetal communications in the circulation of the human foetus are distinctly visualized as well as the various conditions in the cardiac chambers during the cardiac cycle and also its relationship to the circulation in the efferent vessels of the foetus.

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SPANISH ABSTRACT

Estudios Angiocardiográficos sobre la Circulación Fetal Humana—Informe Preliminar

Se describe la angiocardiografía radiográfica directa con 10 exposiciones por segundo en fetus humano en abortos legales. La solución técnica combina las ventajas de una película de alta calidad con una posibilidad de determinar el curso dinámico en el corazón y la circulación en el sistema circulatorio venoso y arterial. Las comunicaciones en la circulación del fetus humano se ven claramente lo mismo que las diferentes condiciones en las cámaras cardíacas durante el ciclo cardíaco y también su relación con la circulación en los vasos eferentes del fetus.

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MINUTE ABSORPTION OF DIPHTHERITIC ANTIBODIES FROM THE GASTROINTESTINAL TRACT IN INFANTS

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MOST children receive, with their mothers' milk, homologous antibodies of various types during the first few months of life. It is a matter of importance to know to what extent these antibodies are absorbed and utilized for protection against bacterial and viral invasions.

In a series of investigations on diphtheria immunity, experiments have been performed with oral administration of homologous diphtheritic antibodies. For practical reasons, human serum was given rather than milk. Although recent investigations[1] have shown that the antibodies from these two different sources are chemically not absolutely identical, evidently they are handled by the organism in the same manner.[2]

Technic and Material

Antidiphtheritic serum was obtained from 6 donors belonging to the staff of the hospital for infectious diseases in Stockholm. The antitoxin titer varied between 2.5 and 5.6 u./cc.

Two different groups of children were investigated, newborns during the 1st wk. of life and older infants between ⅓ and 10 mos. of age. The serum was administered to the infants immediately before meals.

The newborns were all normal infants. Serum dosage was started between 12 and 24 hrs. after birth and continued for 3 or 4 days. The largest amount of serum given at any time was 5 cc.

The older infants represented a mixed group with diagnosis such as prematurity, slightly dyspepsia or social difficulties. They were all, at the time of the investigation, in a satisfactory state of health. The highest amount of serum given as a single dose to these older infants was 35 cc. In 2 experiments the serum was given by duodenal intubation.

Only those infants were accepted for the study who had no measurable diphtheria antitoxin in their blood. For the newborns the serum administration was begun without awaiting the result of titration. It is characteristic of the immunity situation in Sweden at present (Vahlquist[3]) that 15 out of 17 of the newborns thus investigated, by chance, proved to lack completely any specific antibodies against diphtheria.

Determinations of the titer levels were performed according to the method of Jensen[4] with the slight modification that a veronal buffer was used instead of the phosphate buffer originally proposed (Vahlquist and Högstedt[5]). A control series with standard antitoxin is, according to this method, done on every animal to make possible corrections for slight individual differences in the test animals. In order to ascertain the reliability of responses for even minute changes in the titer before and after the serum administration, the blood sample taken before treatment was, in a great number of cases, reanalyzed on the same animal as the blood sample taken after treatment. Direct comparison of the corresponding skin reactions thus made possible was a sensitive guide. Such a comparison is made in the accompanying tables. If the reactions from the 2 sera were completely

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alike ("no qualitative change"), the difference, if any, must have been far below the value 0.0005 u./cc. given as the lowest 1 possible to read by the method.

Results

Results of the administration of serum containing homologous diphtheritic antibodies, either orally or with duodenal intubation, are collected in Tables I and II.

During the newborn period, absorption of antibodies took place to such an extent as to make possible quantitative evaluation in 7 out of 13 cases. Provided the antibodies absorbed are dis-

TABLE I

Effect of Per Oral Administration of Homologous Antibodies Against Diphtheria on Antitoxin Titer of Newborns

Hospital Record No.	Birth Wt.	Total Dose of Antitoxin u.	Antitoxin Titer		Absorption of Antibodies	Quantitative Evaluation of Amount
			Before	After		
1285	2.620	210	<0.0003	≦0.0006	+	≦0.03%
1278	3.200	140	<0.0003	<0.0006	(+)	<0.06%
1282	3.380	140	<0.0003	<0.0003	(+)	<0.03%
1280	3.500	140	<0.0003	<0.003>0.001	+	≦0.30%
1288	3.500	140	<0.0003	<0.0003	0	<0.03%
1287	3.560	210	<0.0003	=0.0015	+	≦0.12%
1293	3.640	140	<0.0003	<0.0003	0	<0.04%
1516	3.670	130	<0.0003	<0.0003	0	<0.04%
1283	3.730	210	<0.0003	≦0.0003	+	≦0.02%
1511	3.960	130	<0.0003	<0.0003	0	<0.04%
1522	4.000	95	<0.0003	=0.0006	+	=0.09%
1510	4.040	130	<0.0003	=0.0003	+	=0.04%
1279	4.040	140	<0.0003	≦0.0003	+	≦0.04%

< means "less than."
> means "more than."

TABLE II

Influence of Per Oral Administration of Homologous Antibodies Against Diphtheria on Antitoxin Titer of Infants Beyond Newborn Period

Group	Number of Experiments	Age of Children in Mos.	Total Dose of Antitoxin/kg. Body Wt.	Mode of Administration	Antitoxin Titer u./cc.		Absorption of Antibodies
					Before	After	
I	2	5–7½	25 A.U.	Duodenal tubage	<0.0005	<0.0005	Qualitatively demonstrable in 1 experiment out of 2 (<0.05%)
II	10	½–10	25–75 A.U.	Per oral (2 days)	<0.0005	<0.0005	Qualitatively demonstrable in 1 experiment out of 10 (<0.02%)
III	2	½–1	117–153 A.U.	Per oral (14 days)	<0.0005	<0.0005	0

tributed throughout a total plasma volume corresponding to 4.5% of the body wt. of the child, the maximal amount absorbed never exceeded 0.30% of the total amount administered. That such a calculation is permissible, that the individual variations in plasma volume in relation to body wt. are not too great, and that there is no important loss of antibodies to the tissues and excreta seems evident from experiments by 1 of the authors (B. V.), which will be published in detail elsewhere. Twenty-four hrs. after the intravenous injection of homologous antibodies in amounts corresponding to 0.005 to 0.02 u./cc. in the blood plasma of the recipient, the same calculation gave on an average 80% recovery.

A "qualitative absorption" could be demonstrated in a further 2 cases. In 4 cases there was no demonstrable evidence of absorption.

The results of antibody administration in older infants were almost completely negative. In only 2 out of 14 cases could an absorption falling below 0.05% be traced. One of these children was the youngest in this older group, 1½ wks. old. The other obtained the serum with duodenal intubation. In all other experiments in this group, 6 of which were titrated before as well as after serum administration on the same animal, no absorption could be detected. This was true also for both experiments with serum administration over a fortnight and for 1 of the 2 with serum administration by duodenal intubation.

Discussion

In experiments with anaphylaxis, it has previously been demonstrated beyond doubt that intact proteins may be absorbed from the gastrointestinal tract in animals as well as in human beings, not only in the first period of life but also later on.[6]

A priori it might be reasonable to assume that these results should apply also to antibodies. According to modern conceptions most antibodies are gamma-globulins. With the aid of electrophoresis, Jameson *et al.*[7] observed in calves fed colostrum from the dam an increase in the gamma-globulin fraction from zero to average adult concentrations within 36 hours after birth. Without colostrum the gamma-globulin fraction appeared slowly, reaching normal values only after many weeks. Recently, Hansen and Phillips[8] have advocated that the capacity of absorption of immune globulins in calves is strictly limited to the first 24 hours of life. In the absence of experiments with duodenal administration, it cannot be known whether the poor absorption later on is due to rapid changes in the absorptive power of the mucosa or to changes in the enzymatic activity of the gastrointestinal tract. It should be noted that the figures given by Hansen and Phillips in their Table II indicate that some absorption may occur also after the first 24 hours.

Polson,[9] in experiments with newborn foals, found the same rapid increase of the gamma-globulin fraction after a few days' suckling.

Conversely to the conditions in the animal species mentioned, the human placenta is easily permeable to most antibodies and sometimes antibody concentrations in the fetal blood are found which correspond rather closely to those of the mother.[10] In conformity with this, Longsworth *et al.*[11] have found normal or even supernormal concentrations of gamma-globulin in blood from the umbilical vein. The further supply of antibodies, regarded from a teleologic point of view, may not be of the same paramount importance to the newborn child.

The literature on antibody absorption in human beings is scanty. Many years ago, Salge[12] reported that he had observed absorption of diphtheritic antibodies from human milk. His studies, however, comprise only three experiments in two children and the results seem unconvincing.

Von Gröer and Kassowitz[13] claimed to have shown, in an indirect way, that specific

antibodies are absorbed in considerable amounts. They investigated the number of Schick negative subjects for breast-fed and bottle-fed infants in different age groups of the first year of life. They found that the number of Schick negative reactors was, throughout, higher in the breast-fed children. Also in this case, however, the results must be subject to criticism, as the breast-fed children in the different groups were usually younger than the bottle-fed ones.

In contrast to these observations, Kuttner and Ratner[14] failed to demonstrate any increase of the diphtheritic antitoxin titer in six newborns after suckling for 6 to 10 days. In their experiments the Kellogg test indicated the presence of diphtheritic antibodies in amounts $\leqq$ 1/30 u./cc. in the colostrum only, not in the milk.

In the experiments with diphtheritic antibodies presented in this paper, the authors have had the advantage of access to an analytic method far more accurate than those in use some decades ago. Furthermore, in the selection of test material due regard has been given to the possibility that the children in the first week of life behave in another way than later in infancy.

In this group of newborns, the administration of serum rich in diphtheritic antibodies started when the child was between 12 and 24 hours old. In the light of recent observations (Hansen and Phillips[8]), it might be questioned if the slight absorption observed in these experiments took place mainly or solely during the first one or two days and hence the percentage figures of absorption for that period should have been a little greater than those calculated from the period as a whole, with a maximum value of 0.30% (Table I). In infants after the first week of life, the absorption of diphtheritic antibodies is evidently negligible (Table II).

Human serum has been used as an antibody source in these experiments. With human colostrum or milk it would have been virtually impossible during the prevailing conditions to achieve antibody quantities large enough. The antibody spectrum of milk reflects that of the mother's blood. In Sweden, at the present time, up to 90% of all adults completely lack specific antibodies against diphtheria in their blood. Such antibodies could therefore appear in the milk at the most in some 10% of all lactating women. The situation might be somewhat different in other countries. But even then the amounts of diphtheritic antitoxin in colostrum and milk are in the great majority of cases small as compared with the amount administered in these experiments. On an average, the concentration of diphtheritic antibodies in human colostrum in a series of Liebling and Schmitz[15] in the United States was 0.01 u./cc. as compared with 1.0 u./cc. in the mother's blood. The concentration was considerably lower than that in the actual milk.

It seems reasonable to assume then that the breast milk should be of little value for the transmission of antibodies against diphtheria. Provided such antibodies are present in human colostrum and milk, they will nevertheless be absorbed only during the first few days of life and even then only in minute amounts.

Summary

Human serum rich in antibodies against diphtheria was given orally to newborns and to older infants. With few exceptions, an absorption of antibodies could be traced only in the first week of life and even then only in minute amounts ($<$0.30% of the total antibody amount administered). The implications of these findings for the value of human milk as an antibody source are discussed.

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SPANISH ABSTRACT

Pequeña Absorción de Anticuerpos de Difteria del Conducto Gastrointestinal en Infantes

Se les administró a infantes recién nacidos y mayores, oralmente, suero humano rico en anticuerpos contra difteria. Con pocas excepciones se pudo ver la absorción de anticuerpos solamente en la primera semana de vida y aún entonces solamente en cantidades pequeñas ($<0.30\%$ de la cantidad total de anticuerpo administrada). Se tratan las deduciones de estos descubrimientos para el valor de la leche humana como una fuente de anticuerpo.

Norrtulls Hospital

RICKETS IN NEWBORN INFANTS

Clinical and Histologic Study

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A PREVIOUS paper[1] established that if premature infants are reared exclusively on human milk the content of calcium and inorganic phosphorus in their serum falls, while the serum phosphatase rises during the first few months of life. If such infants are given large doses of vitamin D in addition to the human milk, the serum calcium will rise while there will be no significant changes in the values of serum inorganic phosphorus and serum phosphatase. If a supplement of cow's milk is given instead, the serum inorganic phosphorus will rise and the serum phosphatase decrease, while the serum calcium will remain about the same as in infants reared exclusively on human milk. Finally, if supplements of both vitamin D and cow's milk are given in addition to the human milk, the serum calcium and serum inorganic phosphorus will rise and the serum phosphatase fall to about the same levels as are found in normal full term breast-fed infants.

In more than half of the roentgen examinations made after the age of one month and occasionally in those made at an earlier age, roentgenologic signs of rickets were found. The infants showing roentgenologic signs of rickets presented much more abnormal serum values than those who were roentgenologically normal. This was true in respect to serum calcium, inorganic phosphorus and phosphatase where the infant had been receiving only human milk, but when vitamin D had been added it was not true in respect to calcium, and when cow's milk had been added, it was not true of inorganic phosphorus or phosphatase.

During the first days of life, premature infants showed significantly lower calcium levels and higher serum phosphatase levels than full term infants, though the values for inorganic phosphorus were about the same. Definite roentgenologic signs of rickets were not observed in any infant less than 14 days old, but in several cases the roentgenograms taken during the first few days of life showed so-called "metaphyseal decalcification." In most of these cases in which metaphyseal decalcification was observed, signs of rickets had appeared by the time the next roentgenogram was taken. One therefore wondered if this roentgenologic sign ought not to be considered as an early sign of rickets. This is in accordance with the interpretation by Graser[2] but not with that of Lindblom.[3]

The findings were interpreted as follows: At birth, the premature infant has insufficient stores of calcium and phosphorus. If it is then fed human milk only, the shortage in phosphorus will become still more marked. This may be compensated for by supplementing with cow's milk, which has a much higher phosphorus content than human milk. On the other hand, the infant usually receives a sufficient supply of calcium

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even with breast milk but it cannot absorb an adequate amount of it unless vitamin D is given at the same time. The deficient supply of phosphorus and the deficient absorption of calcium combined with the insufficient stores at birth may lead to the occurrence of rickets. Thus, rickets occurring in premature infants during the first months of life was considered to be caused, in most cases, by a deficiency of available minerals.

It was, however, necessary to check the conclusion that the chemical and roentgenologic abnormalities observed were really evidence of true rickets by microscopic examinations of histologic specimens. With this in view, costochondral junctions were removed from each infant coming to autopsy at the obstetric department of the Sahlgren Hospital during a period of 2⅓ years (June 1943 to Sept. 1945).

The material is derived from 181 infants. Birth wts. and ages at death are shown in Table I. It will be seen that most of them were premature and that death occurred, in most cases, during the 1st 2 days. Only 26 of them survived more than 15 days and the oldest was 90 days.

TABLE I

DISTRIBUTION OF MATERIAL ACCORDING TO BIRTH WEIGHT AND AGE AT DEATH

Age in Days:	0	1	2–6	7–15	16–	Total
Birth wt.						
–1,000 gm.	19	6	1	1	0	27
1,010–1,500	16	7	8	5	4	40
1,510–2,000	19	6	6	11	15	57
2,010–2,500	4	5	9	8	4	30
2,510–	11	6	6	1	3	27
Total	69	30	30	26	26	181

TABLE II

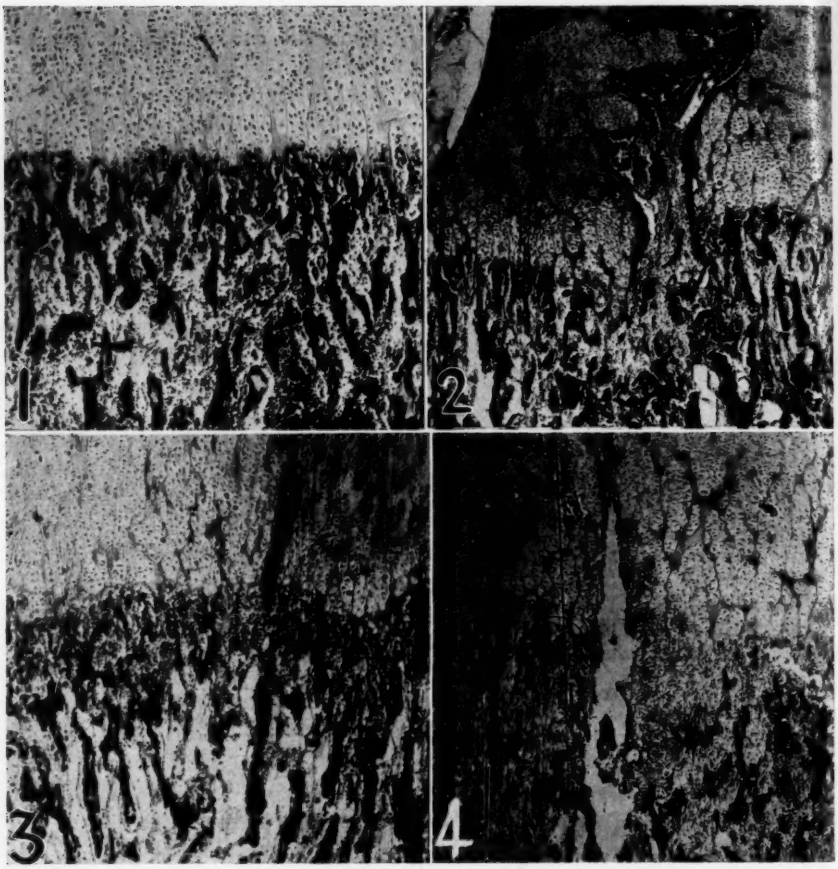
DISTRIBUTION OF MATERIAL ACCORDING TO CAUSES OF DEATH AND AGE AT DEATH

Age in Days:	0	1	2–6	7–15	16–	Total
Cause of death:						
Malformation	6	2	4	3	5	20
Intracranial hemorrhage	16	9	11	2	1	39
Hemorrhage of other organs (suprarenal, hepatic, peritoneal, pulmonary, etc.)	8	2	2	1	3	16
Infection	2	2	5	15	16	40
No cause established. "Asphyxia"	37	15	8	5	1	66
Total	69	30	30	26	26	181

A Wassermann reaction was performed in all cases on the maternal blood during pregnancy or on umbilical blood at birth. In a single case during the 2⅓ yrs. it was found to be positive and this case has been excluded from the material. The series thus contains only Wassermann negative cases.

Table II shows the causes of death where they could be established. The autopsies were performed at the Department of Pathology of the Sahlgren Hospital.

It need hardly be pointed out that only in isolated cases were the infants from whom this material was derived the same as those on whom the clinical observations in the previous paper[1]



FIGS. 1-4. Photomicrographs of cartilage-shaft junction of ribs from 4 infants who died 1st day of life. ×25.

Fig. 1. Structure of normal costochondral junction.

Fig. 2. Early rickets, irregularities of cartilage and bone in cartilage-shaft junction.

Fig. 3. More advanced rickets, increase of width of costochondral junction.

Fig. 4. Severe rickets, pronounced increase of width of costochondral junction with irregular structure of cartilage and osteoid tissue.

had been made. Even if they did not die within the 1st few days of life, they were often so weak from the start that it was not felt justifiable to submit them to feeding experiments or to the necessary examinations. As a consequence, most of the infants in this series received human milk exclusively. Fourteen infants were given supplements of vitamin D for at least 1 wk. and 10 were given various supplements of cow's milk or mineral salts. On histologic examination, these cases showed a similar distribution in the different groups, as did the series as a whole.

One or 2 pieces of rib, including the costochondral junction, were removed from each case (no note was made as to which bone or bones these pieces were removed from). The material was fixed in 10% formalin. It was decalcified by standing in nitric acid for 48 hrs. according to the method then current in this Institute. The preparations were then embedded in paraffin. The sections

were cut at right angles to the costochondral junction and to the flat surfaces of the rib. They were stained with hematoxylin and van Gieson's stain.

Owing to the excessive decalcification of the preparations, the sections were not suitable for demonstrating the earliest changes associated with rickets, namely, defective lime salt deposition in normally constructed bone. The observations were, therefore, limited to the recording of irregularities in the costochondral junction, i.e., irregularities in the structure of the cartilage, bone and osteoid tissue at the junctions, and also the development of osteoid tissue with increase of width of the cartilage-shaft junction.

Those cases showing definite rachitic changes of the sort just mentioned were described as + while those showing a normally constructed costochondral junction were described as —. The material naturally included all transitional forms between clearly positive and clearly negative cases. However, it appeared that those cases which would, on histologic grounds, have been described as (+) or ? were distributed throughout the different groups of the material roughly in the same way as the definitely negative cases. These doubtful cases have, therefore, been included for the present among the cases described as —. These cases which were originally described as (+) or ? must

TABLE III

INCIDENCE OF RICKETS IN DIFFERENT AGE GROUPS

Age in Days	0	1	2–6	7–15	16–	Total
No definite rickets	49	15	7	3	4	78
Definite rachitic changes	20	15	23	23	22	103
per cent	*35.4%*			*83.0%*		*56.9%*
Total	69	30	30	26	26	181

undoubtedly include some early or mild cases of rickets. The figures given below for the incidence of rickets are thus minimum figures; they refer to the incidence of rickets which is so far advanced from a histologic point of view as to present gross structural irregularities in the costochondral junctions.

There were also, of course, variations from case to case in the degree of severity of rickets in the cases described as +. Figs. 2-4 show examples of different histologic degrees of rickets for comparison with Fig. 1 which shows a normally constructed costochondral junction.

It appears from Table III that cases showing definite rachitic changes are not uncommon during the 1st 2 days of life, and from as early as the 3rd day onwards they form the majority. During the 1st 24 hrs. more than ⅔ of the cases appear free from rickets, and during the 2nd day, half, but after that the great majority show definite signs of rickets. The difference between the incidence of rickets during the 1st 2 days of life and during the subsequent periods is statistically highly significant ($47.6 \pm 6.35\%$).

While it was to be expected that the incidence of rickets would rise with increasing age, it was scarcely expected that it would rise so fast or that so many cases of rickets would be demonstrable even in the first few days of life. According to current textbooks, congenital rickets is a rare condition and it is even questioned whether it occurs except in children of mothers with osteomalacia. Rarely is any other opinion met with in the literature.[2,4] However, few studies have been published concerning the frequency of rickets in histologic preparations from young infants. In fact, only two such investigations of any size seem to have appeared: that of Schmorl in 1907[5] and that of Follis, Jackson, Eliot and Park,[6–8] which is as yet only partially published. Schmorl's series does not include infants of less than two months old, but he states that he has never seen rachitic changes in infants before the latter half of the second month of life. During the third

month, he found rickets in 61% of the cases; after that the incidence rose to a maximum of 98%. In the American series, rickets was found in 21% of 90 cases during the first month of life. During the second month, the frequency rose to 48%. The youngest child with rickets in the American series was 10 days old. It is not clear, however, from what has been published hitherto, whether still younger infants are included in the material.

Of the infants included in the series presented here, 173 were less than 30 days old and of these 98 (56.7%) showed definite rachitic changes. For the 146 premature infants less than 30 days old the corresponding figure is 80 infants (54.8%), which is about the same. Histologic findings on material from premature infants do not appear to have been described previously.

The most surprising feature of these results is that no less than 35.4% of the infants dying within two days of birth showed definite signs of rickets. At least in those infants who died during the first day of life, the rickets must be regarded as congenital.

Moreover, the mothers of the infants in the series were certainly not suffering from osteomalacia. They might be regarded as forming a fairly representative cross section of the population of Gothenburg. Many of them belonged to the lowest social class but in no case can the standard of living be compared with that of the Indian or Japanese women with osteomalacia. A study of the accounts given by the women themselves of their diet during pregnancy reveals generally a satisfactory situation; all stated that they had consumed a lot of milk, usually between ½ and 1½ liters a day. The only fault was that a great many of them had not taken any vitamin D supplement. No correlation was found between a low consumption of vitamin D by the mother and rickets in the infant. Of 73 mothers who gave unequivocal reports of their vitamin D consumption, only 21 had taken the customary amounts for at least two months during pregnancy. The percentage of infants with definite rachitic changes was the same for these 21 as for all the 73 mothers. Children born in the summer were found to have rickets somewhat less frequently (minimum May-July, 50%) than those born in the winter (maximum December-February, 63%) but the difference was not statistically significant (diff. $= 13 \pm 10.1\%$).

There seems to be a certain correlation between the length of the pregnancy and the incidence of rickets in that children born after a pregnancy of less than 28 weeks seem to have rickets less often than the more mature infants (29 and 60%, respectively; diff. $= 31 \pm 9.8\%$). There was, however, no significant difference in the incidence either between the children born after a pregnancy of 28 to 31 weeks and those born after a longer pregnancy, or between those born after a pregnancy of 28 to 35 weeks and those born after the 35th week. These facts indicate that the rachitic changes demonstrable at birth usually develop during the latter part of the pregnancy.

From this it seems evident that rachitic changes appear considerably earlier than has hitherto been believed and in many cases are present even at birth. This is true not only of premature infants but also of full term ones. This series of full term infants is admittedly small, but in it the incidence of rickets is even greater than in the total series, 63.0% as against 56.9%. The difference, however, is not statistically significant in this small material. These observations may be of practical importance in that they transfer a larger amount of the responsibility for the prevention of rickets on the obstetrician than hitherto.

The frequent occurrence of histologically demonstrable rickets observed in this study lends support to the assumption that the chemical and roentgenologic changes described in the previous paper[1] are really rachitic in nature and, therefore, also supports the conclusions drawn in that paper, that the insufficient stores of calcium and phosphorus present at birth, at least in premature infants, combined with insufficient consumption of phosphorus in breast feeding and insufficient absorption of calcium may be the cause of the rapid increase of the incidence of rickets immediately after birth.

Summary

In a series of 181 consecutive cases of infants who had died soon after birth, 103 (56.9%) showed definite histologic signs of rickets. Of the 69 infants dying during the first day of life, 20 (29%) had rachitic changes and in these the rickets must be regarded as congenital. Of the 181 cases, 154 were premature, weighing less than 2,500 gm. at birth. The incidence of rickets was about the same in the premature and the full term infants in this material. The incidence of rickets increases rapidly with increasing age during the first weeks of life.

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Spanish Abstract

Raquitismo en Infantes Recién Nacidos y Prematuros Estudio Clínico e Histológico

En una serie de 181 casos consecutivos de infantes que habían muerto pronto después del nacimiento, 103 (56.9%) mostraron señas histológicas definitivas de raquitismo. De los 69 infantes que murieron el primer día de vida, 20 (29%) tuvieron cambios raquíticos y en éstos el raquitismo se debe considerar como congénito. De los 181 casos, 154 fueron prematuros, pesando menos de 2,500 gm. en el parto. La incidencia del raquitismo fué poco más o menos la misma en los infantes prematuros y en los normales en este material. La incidencia del raquitismo aumenta rapidamente con la edad durante ls primeras semanas de vida.

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MIXED INFECTION OF HEMOLYTIC STREPTOCOCCI IN CASES OF PRIMARY TUBERCULOSIS IN CHILDREN

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PUBLICATIONS dealing with antistreptolysin titer (AST) in healthy subjects, both children and adults, show varying figures for the frequency of pathologically raised titers; i.e., over 200 A. U. (the normal limit generally agreed upon).

The variations of AST both in healthy and sick persons must be viewed in the light of the incidence of hemolytic streptococci in healthy subjects.

Table I gives a survey of the occurrence of hemolytic streptococci in healthy subjects from certain cities and countries.

Only investigations where the capacity of the strains to form streptolysins has been

TABLE I

Place	Category	Number	Str. Hemolyticus %	Group A %	Author	Year
U.S.A.	Students	621	16. 2	6. 4	Frisch[1]	1938
Copenhagen	Children	100	23	16	Kalbak[2]	1942
London	Schoolchildren	2048	13. 3	10. 4	Lancet[3]	1947
Stockholm	Adults	309	14. 2	10	Lagercrantz[4]	1948

examined have been included in the table. The great majority, 95%, of the chief hemolytic streptococci that breed disease in man may be ranged (according to Hare[5]) in Lancefield's serologic group A, the others in groups C and G. The frequency of group A is indicated in the table.

Among the factors that are considered to affect the occurrence of hemolytic streptococci, the following may be mentioned (quoted from Lagercrantz[4]):

1. Climate. The further from the equator, the more numerous the carriers of streptococci.

2. Season. A greater number of carriers are found during winter and early spring than in other seasons.

3. Environment. A greater number of carriers are found in towns and in crowded establishments, such as military encampments and schools.

4. Certain ages. Children, especially between the ages of 7 and 10 years, are more often carriers than adults.

5. Epidemiologic factors. A larger number of carriers are found during epidemics caused by streptococci.

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6. Status in pharynx. Persons who have recently had a pharyngeal infection more often show streptococci than others. Persons whose tonsils have been excised less often show streptococci than others.

7. Investigation technic. Some streptococci grow typically only in primary anaerobic cultures. Repeated tests and concentration substrates give a considerably larger yield.

The incidence of antistreptolysin in healthy subjects is shown in Table II. The variations are considerable. From 3 to 16% of the cases show an AST of over 200. In the Scandinavian groups the figures range between 11 and 16%.

As the present work relates mainly to primary tuberculosis in children, a survey is given of the principal investigations hitherto published in Sweden, where, in the course of the last five years, the question of mixed or multiple infections in cases of tuberculosis has been receiving great attention.

TABLE II

Investigator and Year	Number	Category	Percentage of Subjects Grouped by AST Values:		
			0–99	100–199	≧200
Coburn and Pauli 1935[6]	320	Children and adults	77	17	6
Gordon and Baltenau 1938[7]	316	Children	77	20	3
Kalbak 1942[2]	200	Children	64	25	11
Lagercrantz 1948[4]	398	Adults	44	40	16

As far back as 1884, Robert Koch[8] had observed at autopsy how frequent nonspecific infections were in cases of tuberculosis, but for the next 50 years research on this question had not led to any definite conclusions. Due to the clinical observations of Westergren in particular, this problem has again been brought into the foreground. Bacteriologic and serologic investigations on adults made by that author and corroborated by others have shown the correctness of these observations.

Westergren[9,10] found in 360 cases of pulmonary tuberculosis that the antistreptolysin titer was over 200 in 35.5% of the cases. Among 534 cases of acute tuberculous pleurisy, this titer was raised in 43.6%. The antistaphylolysin titer (ASTA) in 56.2% of the cases was over 1.0 A. U., a figure that had been taken as a normal limit. Cases of simple glandular tuberculosis, i.e., without parenchymatous processes, showed the highest frequencies, 61.9 and 67.7% of the said titers (AST and ASTA), respectively.

Packalén[11] found, among 179 tuberculous patients without clinical symptoms of streptococcal infection, the AST raised in 49% of the cases and hemolytic streptococci in the pharynx in 34%.

Löfgren,[12] in his investigation into erythema nodosum, found the AST raised in 32.6 ± 5.1% of the cases with tuberculous etiology. Only 16.9% of his control group of healthy subjects had a raised AST. The difference is statistically probable. Löfgren[13] showed that the cases of erythema nodosum formed a special group with a higher frequency of multiple infections than the cases of primary tuberculosis without erythema nodosum. Moreover, he showed that the prognosis for primary tuberculosis in adults with erythema nodosum was worse than for cases without that complication. The difference has been confirmed by statistics.

Stavenow[14] found a raised AST in 30% out of 1471 cases of pulmonary tuberculosis. In 190 of these cases, the ASTA was pathologically raised in 45.8%. The frequency of raised titers was higher in patients with indubitably active, progressive parenchymatous changes than in other cases.

Winblad[15] found a raised AST in 40% of the cases with erythema nodosum of tuberculous etiology.

Adamson,[16] having made a bacteriologic study of the lymph nodes on postmortem material, found in cases of tuberculosis an abundant mixed infection flora containing β-hemolytic streptococci, staphylococcus aureus, Bacillus coli, pneumococci and other bacteria. In the control material (such as cases without appreciable organic disease or infection, cases of medical jurisprudence and traffic accidents) the mixed infections were few. The difference with regard to β-hemolytic streptococci and staphylococci was confirmed by statistics.

On the basis of these reports, the authors contend that nonspecific infections should be regarded as of primary importance for the onset, development and course of the tuberculous disease.

All the above-reported investigations have been carried out on adults. In order to obtain an idea as to the corresponding conditions in children, the antistreptolysin material in cases of primary tuberculosis at the Norrtulls Hospital for children has been studied. Owing to the difficulty of obtaining sufficient blood from infants, the tests were rather irregular during the first few years, but since the adoption of a micromethod the determinations have been made every other week.

The material comprises 190 cases of primary tuberculosis in children from Stockholm, aged 1 to 15 yrs. As only indubitable titration values have been included, namely, cases where at least 2 determinations have been made, the AST material has been reduced to 130 cases. Owing to the possibility of errors in the readings, e.g., where the variations range from −50% to +100% (Lagercrantz[4]), a single value must be regarded as unreliable, unless it is very high or very low.

The cases have been divided into 4 groups, according to the age and type of the processes. Group A comprises cases of primary tuberculosis in the initial fever stage. Group B comprises cases with a primary tuberculous process not older than 3 mos., but where the initial stage had been passed. Group C comprises processes aged over 3 mos. Group D, finally, comprises cases of primary tuberculosis which had originated with an onset of erythema nodosum. The occurrence of Str. hemolyticus in the pharynx is shown in Table III.

TABLE III

Group	Total Cases	Cases with Str. hemolyticus	Case Percentage
A	43	11	25.6
B	51	15	29.4
C	54	15	27.8
D	42	21	50

Compared with the frequency of Str. hemolyticus in healthy subjects, the figures for groups A, B, C are nearly twice as high as in Lagercrantz's investigation in Stockholm. Group D (the cases with erythema nodosum), on the other hand, holds a distinct position with no less than 50% Str. hemolyticus. Löfgren's investigation on adults, as previously mentioned, yielded a similar result.

The result of the AST investigation is shown in Table IV.

As compared with the figures for healthy subjects (Table II), with regard to AST over 200, an

TABLE IV

Group	No. Cases	0–99	100–199	≧200	Percentage AST ≧200
A	26	13		13	50
B	38	17	7	14	36.8
C	29	9	6	14	48.3
D	37	8	4	25	67.6

TABLE V

Group	No. Cases	0–99	100–199	≧200	Percentage AST ≧200
A+B	64	30	7	27	42.2
D	37	8	4	25	67.6

increase of more than double is noted. If groups A and B, in this table being approximately similar to group D in regard to the age of the processes, are added together and compared with group D, the results are as shown in Table V.

The difference is statistically probable (25.4 ± 9.85).

It would be of interest to see whether the frequency of complications in cases of primary tuberculosis differs in different AST groups. The time during which these cases have hitherto been kept under observation is still too short to admit of any reliable figures. A previous investigation in 1947 showed that among 18 cases of tuberculous pleurisy 11 had an AST of over 200, but the number of cases is, of course, too small to serve as a basis for any conclusions.

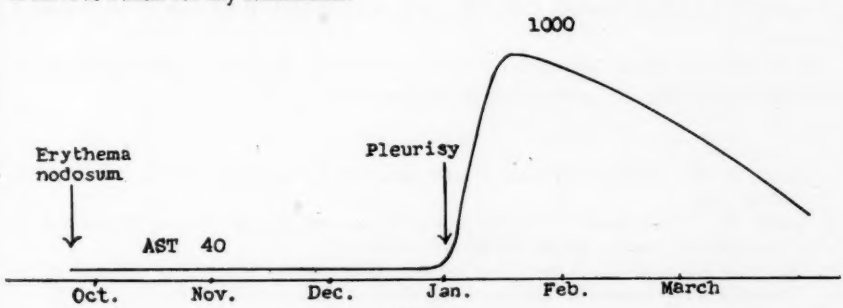

CHART I

In this connection a case of pleurisy, treated at the Norrtulls Hospital for Children, may be of some interest. The patient was a five year old boy, who at the end of September 1946 was ill with high fever. He was treated with sulphathiazole and a few days later developed nodal fever, because of which a tuberculin test was made; it was then positive, whereas it had previously been negative. The roentgenogram revealed an early case of primary pulmonary tuberculosis. He was confined to bed at the hospital during the months of October, November and December and had an AST that kept steadily at about 40. Hemolytic streptococci were never detected in the pharynx. On the first of

January, he developed a massive pleurisy. The day after the AST had risen to 80 and, as shown by Chart I, mounted on the 14th of that month up to 1,000. In the course of the following months, however, it gradually fell to 200. In December 1946, many members of the hospital staff were infected with hemolytic streptococci and the boy himself developed pharyngitis towards the end of that month. There were several similar cases where the patients had developed pleurisy at the hospital and where they had a raised AST in connection therewith. On the other hand, there were several cases with a distinct massive pleurisy, but without a rise of the AST.

The results of this investigation indicate that mixed infection with hemolytic streptococci is widespread, even in children with primary tuberculosis, and that cases which start with erythema nodosum hold a special position, with a high frequency of streptococcal infections.

As a consequence of the evidence mentioned in the introduction to this paper and the results obtained in the study above described, we have started to give penicillin for about a week to those patients with primary tuberculosis who have either a spontaneous erythema nodosum or a high antistreptolysin or antistaphylolysin titer.

Summary

A survey of the literature on the occurrence of hemolytic streptococci and antistreptolysin in healthy subjects and on recent investigations of mixed infections in tuberculosis is discussed.

Among 190 cases of primary tuberculosis in children aged 1 to 15 years Str. hemolyticus were found in the pharynx and among 130 such cases antistreptolysin titers over 200 were found to be considerably more frequent than in healthy children or other healthy subjects.

Cases of primary tuberculosis where the symptom first manifested had been an eruption of erythema nodosum formed a special group, with a high frequency of streptococcal infection.

Cases with erythema nodosum or with a pathologically raised antistreptolysin or antistaphylolysin titer are given a course of penicillin.

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SPANISH ABSTRACT

Infección Mezclada de Estreptococos Hemolíticos en Casos de Tuberculosis Primaria en Niños

Se trata de un estudio de la literature en el caso de estreptococo homolítico y la antiestreptolisina en personas sanas y recientes investigaciones de infecciones mezcladas en tuberculosis.

En los 190 casos de tuberculosis primaria en niños de la 15 años, se encontraron estreptococos hemolíticos en la faringe y en 130 de tales casos se encontró que los títulos antiestreptolisinos de más de 200 eran considerablemente más frecuentes que en niños sanos o en personas sanas.

Los casos de tuberculosis primaria donde los síntomas se manifestaron primero habían sido una erupción de eritema nudosa formaron un grupo especial, con una frecuencia alta de infección estreptocóccica.

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THUMBSUCKING; FREQUENCY AND ETIOLOGY

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THUMBSUCKING is, in widespread circles, considered a pernicious habit. Herein lies an ethical evaluation. Morals have little in common with biology and are a hindrance to medical research work as they introduce factors changing with the times and in different peoples and also varying in different social strata. Some centuries ago, children who took solace in thumbsucking were regarded with complacency. Artists used them as subjects for pictures expressing peace and sublime tranquility.[1] One may assume that thumbsucking has been considered a problem only during the last century. A powerful support in combatting the habit was obtained from dentists, who in the '20's claimed that deformities of the jaws and malocclusions might be the result of prolonged intensive sucking.[2-4] It has been assumed that oral and intestinal infections also might be sequelae.

Since thumbsucking was considered a bad habit, it was long combatted on the same lines that usually are followed in the case of other habit addictions: with nagging, remonstrances, threats, intimidations and coercion. The underlying causative factors were not sought for, and the measures were stamped by an arbitrary opinion, coupled with an experience which, however, was ambiguous, as there was success in breaking the habit in a number of cases without apparent complications, while in other cases the thumbsucking was cured but symptoms of restlessness of varying degree appeared instead—and in still other cases there was complete failure.

When a search began to be made for the cause, psychoanalysis appears to have directed the line of thought. Freud's emphasis on the importance of the oral zone for the gratification of the instincts of the infant implied not only the craving for food but also that for sucking. Whether this craving for sucking, which unquestionably is present, is primary has not as yet been made clear; although much has been written on the subject, only little has been investigated.[5] The question of whether a requirement for sucking, distinct from the appeasement of hunger, is present at birth is not of decisive importance for the problem of thumbsucking. It has been established that there is a sucking reflex with potentialities of thumbsucking already in fetal life.[6] It has also been established that this reflex is stimulated with varying ease and to varying degrees of intensity under different conditions of wakefulness and satiation.[7]

In the investigation on the basis of which Levy[8] in 1928 stressed the primary influence of the sucking period on thumbsucking, there is also the observation that occasionally apparently adequate breast feeding is not an infallible prophylactic against thumbsucking.

The subsequent investigations of Levy[9] on puppies that were raised without being permitted to suck and that developed into "paw-suckers" seems suggestive, but is contradicted by the fact that a number of children raised by spoon feeding and who thus had an inadequate sucking activity have not become thumbsuckers.

Gesell[6] lays emphasis on the normal developmental trait which he calls hand-to-mouth reaction. When the maturation of the nervous system has advanced so far as the age of

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three or four months that the infant can manipulate its hands and arms, there appears a normal tendency to raise them to the mouth and there liberate the sucking reflex. Thumbsucking is thus, according to Gesell, an entirely normal phenomenon, a stage of development which should be passed by the second to third year of life. Sporadic relapses may occur on local irritation of the mouth such as teething, or if, for some reason or other, the interest and attention of the child are directed from a normal and healthy extrospective activity to the child himself. Gesell thus does not attach much importance to the mode of feeding and the duration of the sucking phase of the feeding act.

Several other American pediatricians and child psychiatrists have contributed studies but definite agreement has not been reached.[10,11] It has seemed to be of interest to throw light upon the relationship of thumbsucking to feeding and the frequency of the habit by an investigation on the normal urban children of a child health center.

Definition

Thumbsucking is hereby interpreted as all habitual sucking on thumb, other fingers, a lock of hair, a sleeve, pillow, sheet, blanket or toys, this sucking taking place while dozing off, or during sleep or at any time of the day when there arises need for solace. The entirely dominant factor is the sucking, which has given rise to the nomenclature. Thumbsucking which has been discontinued prior to one year of age has not been taken into account as this is considered an entirely normal phenomenon.

Basic Material

The mothers of all of the children born between 1941 and 1944 under supervision at the child health center were given a questionnaire and were requested to answer detailed questions relevant to feeding, thumbsucking and so forth. The reports were checked with the case records and notes and through personal interviews. The author has from 1944 to 1945 taken continuous notes, not only with regard to the somatic aspects but also, as far as has been possible, short notes on mild or more severe behaviour disturbances, thumbsucking, nailbiting and so forth. It has not been possible to elicit a complete response from all the mothers and this has been taken into consideration in the calculations. The investigations were carried out in 1948.

In the age groups 1942 to 1944, the response to the questionnaire was practically 100%, thus making it feasible to obtain a reliable figure on the prevalence of the habit. The children were derived from the socio-economic strata of the laborer and the lower middle class and registration at the child health center in this geographically well defined district of the capital (Lilla Essingen) is high.

The questions to be answered in the form were: whether the child was or had been a thumbsucker before falling asleep, at night, during the daytime, or at home or out of doors; if the habit had been discontinued, then at what age, and whether it had ceased voluntarily or because of some measure and, in that event, what measure. Whether there were any noticeable sequelae to the termination; if the thumbsucking had continued, whether any measures had been tried without success. When the thumbsucking started. Furthermore, the conditions at feeding, the duration of breast feeding, bottle feeding, spoon feeding, the approximate period of time during which the child was permitted to suck at its meals; whether he seemed satiated or habitually began thumbsucking immediately after the meal. Whether the child had had a dummy teat (pacifier) and, in that event, for how long. The answers have been corrected and checked with the aid of

the records. The mothers were asked only to notate facts of which they were definitely certain.

Frequency

Out of the 259 children between four and six years of age, 130 had never sucked fingers to such an extent that they could be characterized as thumbsuckers. The distribution was equal in all the age groups, approximately 50%. The frequency decreased slowly during the years. If, at the age of one year, one half of the children were thumbsuckers, the figures for the two year olds were 47%, for the three year olds 42%, for the four year olds 36%, for the five year olds 30% and for the six year olds (the oldest age group) 21%. These figures include all the degrees of intensity of thumbsucking. As late as at the age of four years, 14% of the children were classified as intensive thumbsuckers.

Point of Time of the Onset of the Habit

In approximately 100 cases for whom it has been possible to establish the onset of the habit with reasonable accuracy, the time was:

Prior to 3 mos. of age	54%
Prior to 3-5 mos. of age	22%
Prior to 6-9 mos. of age	14%
Later	10%

Correlation of Feeding to Thumbsucking

An attempt was first made to analyze whether those who were thumbsuckers at one year of age showed any difference with regard to breast feeding or bottle feeding from those who never had been thumbsuckers. No statistically significant difference was established between the number of thumbsuckers and nonthumbsuckers among the children who had been breast-fed for six months or more. Neither was there any statistically significant difference between those who for six months had received either mixed feeding or formula by bottle alone. Among those who to some extent had been spoon-fed there was an insignificantly greater number of thumbsuckers than of nonthumbsuckers.

The next correlation did not have a bearing on the duration in months of the phase of breast or bottle feeding but on the average duration of each meal. This was generally reported as 20 minutes (175 cases), and there was hereby a fairly equal distribution of suckers and nonsuckers. Among those (24 cases) with a strikingly short meal time, 14 were thumbsuckers and 10 were nonthumbsuckers. Among those who had been breast-fed or bottle-fed for more than 20 minutes there was hardly any demonstrable difference. But in this group of children with protracted meal times, there are also included cases in which the breast feeding always had been troublesome, where the child constantly had refused the breast and the entire process had stretched out over a considerable period of time at every meal and also those children who, notwithstanding a prolonged breast feeding, immediately after each meal had demonstrated insufficient sucking by stuffing the fist or fingers into their mouth. If these cases are rejected from the group, then for the uncomplicated long-suckers, the frequency of nonthumbsuckers is twice that of the suckers.

Dummy Teat

Thirty-two children had constantly used a dummy teat over a more or less lengthy period of time. Among those who had used the teat for over three months (28 cases the

greater part of the first year of life), there were no thumbsuckers. In two of the remaining cases who used the teat for a short time only, the sucking had commenced in association with giving up the teat, and in the last two cases the habit had begun several months later.

Intensive Thumbsuckers

Mild and transient dozing-off suckers have with regard to frequency and correlation figures been compared with intensive daytime suckers. Common for both groups is that they habitually sucked fingers at least at one year of age at some period of the day or night. This is thus a heterogeneous group. With the object of making a more selective comparison between thumbsuckers and nonthumbsuckers, all those who at least at the age of four have sucked fingers not merely when falling asleep but also when confronted with the various problems of the day have been gathered into one group. As an unselected control group of nonsuckers, children from the child health center of comparable ages were used.

The group of intensive thumbsuckers at least four years of age comprised 39 cases. In eight of the cases, the reports were insufficient to permit of a correct estimation of the feeding. Out of the remaining cases, there were only eight instances of apparently uncomplicated feeding, lasting at least approximately 20 minutes for each meal at the breast or by bottle (sucking in both cases), over a period of at least six months. The 23 remaining cases were restricted in one way or another. In the nonthumbsucker control group the figures were entirely reversed, 23 cases having had an uncomplicated feeding, while the remaining eight cases had not.

Comments

It is often difficult to arrive at an opinion regarding feeding under home conditions and to what extent the child has had a satisfactory sucking phase. Where mothers are familiar with the physician's definite injunctions (feeding periods at regular intervals and of the same duration), these injunctions may influence the veracity of the reports. Some mothers seem to have an urge to emphasize their capacity for giving a protracted breast feeding, feeling their own importance increased hereby. However, the author by a specific technic in interviewing and by control measures has sought to restrict these errors to a minimum.

It thus seems to appear from the investigation that the satisfaction of the sucking activity is a factor, but not the only factor, in the etiology of thumbsucking. The effect of a dummy teat is particularly conspicuous and suggestive. None of the 28 children who used a dummy teat during the major part of the first year of life were thumbsuckers. The reason for this, besides the gratification of the sucking requirement, may be that the teat eliminates the rooted reaction patterns which are developed in fingersucking by the need for solace and sucking. If the same need should arise in those who give up the teat after the age of one year, they do not have the same rooted habits at their command as do the thumbsuckers. The former teatsucker must seek other solace, more adequate for his age. In view of this result, one must question whether the employment of a dummy teat has such drawbacks that it should be discouraged at the risk of provoking the habit of thumbsucking. It is therefore the hygienic aspect which is of importance, other factors being irrelevant. But the thumb is a dirty, bacterially contaminated organ, most of all when the hand begins to be used for purposes of examination and support. According to Barton,[12] the thumb actually was more contaminated than the teat used. The bacterial colonies were 10 times more frequent in smears from the thumb than from the teat. There has been no

difficulty in discarding the dummy teat in these cases and the process has not required as much effort as has breaking the habit of thumbsucking.

Since 50% of the children have never been thumbsuckers and the teatsuckers only comprise a scant third of these, it is obvious that there are other and more important factors which counteract the acquisition of the habit. It is reasonable to assume that the natural sucking activity at the breast is the foremost of these factors. The bottle-fed child seems largely to be on a par with the breast-fed child in this respect. But we must not overlook that there are among the thumksucking children individuals who, as far as can be ascertained, have had a prolonged and satisfactory sucking period at feeding time, at least according to current pediatric requirements, and that nonsuckers in some instances seem to have had an unsatisfactory feeding situation. This phenomenon still remains to be explained. I will here merely outline some possibilities.

In the first place, it is known that infants have highly varying nutritional requirements. Of two children of the same age, one may need twice the amount of food in order to arrive at a satisfactory increase of weight.[13] This fact, in the case of the hungry child of an overzealous mother who anxiously keeps watch that the grams of food received do not exceed the amount permitted, may favor thumbsucking. In the second place, it is probable that the factor "sucking requirement" is constitutionally different. Some children are more easily satisfied than others and, if the satisfaction coincides with the more palpable bodily repletion, thumbsucking need not arise. Thirdly, the etiology outlined by Gesell seems to stand uncontradicted in a number of cases. What is valid here mainly is the observation that the difficulties in the educational situation of the one, two or three year old with severe emotional stress are liable to make him keep up the major comforting function of the infant age. This implies a step backwards in emotional development, a regression, such as has been described in the course of child analyses.

Routine Methods of Treatment

The therapeutic requisites embrace a wide register, as in the case of many other stubborn behaviour disturbances attached to unsatisfied needs. The hitherto prevalent measures of treatment may be divided into 3 groups:

1. Threats, nagging, admonitions (from the simple "don't" to the alarming perspective "the thumb will fall off if you persist.").

2. Restrictive mechanical measures, eventually in combination with sedatives to counteract the restlessness expected to result from the restraint (mittens, bandages, finger-cots, cardboard discs, cuffs, and so forth).

3. Attempts to cause distaste for the thumb by application of bitter and nasty-tasting mediums (such as pepper, colocynth or quinine, vinegar, mustard, "Finger Tip").

The results of treatment have in the present series been poor. In those cases in which the thumbsucking has ceased, this has more commonly taken place without any special measures than it has following an intervention. In some cases, however, restraint has been successful but not infrequently it has had injurious effects. The most common of these is difficulty in falling asleep, and there are reports that the children in association with the measures taken have become nervous and restless, "hysterical" cry-babies, or nailbiters. In isolated cases there has been enuresis or jactitation. One may advance the assumption that in those cases in which the treatment has met with success the craving was less markedly developed so that the treatment merely was felt slightly and that in these cases the thumbsucking soon would have ceased in any case.

It is necessary in this connection to mention briefly the problem of deformities of the teeth and jaw which are the most important indications for treatment. A deformation may undoubtedly be the result of thumbsucking, even though many constitutional malocclusions have been ascribed to this habit. But dental orthopedic investigations have also established the strong inherent power of spontaneous normalization of the growing jaw when the pathologic pressure, caused by the sucking, gradually disappears. The frequency of deformations of the present series has not been subject to investigation.

The author gives warning against that form of nihilistic concept of the treatment which typically is expressed by the pronouncement, "he will outgrow the habit," upon which nothing is done. This attitude, however, is probably better than the strong-hand measures. There are usually a number of environmental factors that primarily should be corrected so that the child will be in less need of solace.

Summary

The investigation was carried out for the purpose of establishing the frequency of thumbsucking and the importance of the sucking factor for the etiology. Thumbsucking and other comparable sucking occurred at the age level of one year in 50% of the cases. At the age of four years there was a frequency of 36%. These figures include both the mild and the more severe degrees of thumbsucking. If only the latter are taken into account the figure for age four is about 14%. One of the primary determinant factors in the arisal of the habit, as far as can be judged, is the degree of satiation in infants of the sucking activity. The probability of this appeared from comparisons of the mode of feeding. In any event, none of the at least four year old children who had used a dummy teat (rather more than 10% of the entire series) had ever been thumbsuckers.

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SPANISH ABSTRACT

Chupadura del Pulgar; Etiología y Frecuencia

Se llevó a cabo una investigación con el fin de establecer la frecuencia de la chupadura del pulgar y la importancia del factor de chupar para la etiología. La chupadura del pulgar y otras chupaduras comparables ocurrieron a la edad de 1 año en 50% de los casos. A la edad de 4 años había una frecuencia de 36%. Estas cifras indican los grados suaves y más severos de la chupadura del pulgar. Si solamente este último se toma en consideración, la cifra a la edad de 4 años es aproximadamente 14%. Uno de los factores determinantes principales en el hábito, según se puede juzgar, es el grado de saciedad en los infantes de la actividad de mamar. La probabilidad de esto apareció de comparaciones del modo de alimentación. En todo caso, ninguno de los niños de 4 años que habían usado la imitación de teta (más del 10% de toda la serie) han sido chupadores del pulgar.

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THE SWEDISH BCG EXPEDITION IN GERMANY

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IN SIMILARITY with conditions in other war-harassed countries, there was a great increase of tuberculosis in Germany during and immediately after World War II. Lydtin[1] reports that the mortality in 1946 showed an increase of between 50 and 100% as compared with the prewar mortality rates. Children in the first three years of life and young people in ages ranging from 15 to 25 years especially fell victim to the disease. Owing to the lack of hospital accommodations and material for roentgenographic examinations, the Germans after the war had no possibility of treating or of isolating and supervising all these tuberculous cases. If to this there is added the appallingly overcrowded living-quarters of the bomb-damaged German towns and the inherent risk of contagion, one understands the apprehension of the German medical profession that the tuberculosis mortality rate, which since 1946 had seemed to be on the decrease, would again rise. It was therefore with deep appreciation that the Occupation Forces and the German authorities received an offer of assistance for BCG vaccination from the Danish and the Swedish Red Cross. After the war, there had been organized on the initiative of the Danish Red Cross and UNICEF a cooperation, for the purpose of fighting tuberculosis, between the Red Cross Associations of the Scandinavian countries, Denmark, Norway and Sweden, the only countries in which there is a long-standing and extensive experience with BCG vaccination. Physicians, nurses, vaccine and other materials for vaccination were accordingly sent to Germany. In 1947 the Danish Red Cross commenced BCG vaccinations in the American zone and in Schleswig-Holstein and in June 1948 the Swedish Red Cross commenced its task in the British zone. This Swedish action and some of the experiences gained from it will be reported in this paper.

The Swedish personnel consisted initially of a physician-in-chief and a vaccination group of one physician and two nurses, all trained vaccinators. While organizing a sweeping campaign for the vaccination of school children in close collaboration with the German authorities, the Swedish group tuberculin tested and vaccinated German students in Münster, Bonn, Cologne, Düsseldorf, Göttingen and Aachen, and, also, in collaboration with the physicians of the displaced persons' camps, the children and youth in these camps up to 25 years of age.

When the vaccination of school children was begun in September, approximately 5,000 students had been tuberculin tested and more than 1,000 had been vaccinated. In the DP camps, the corresponding figures were 4,000 and 2,000, respectively. The participation among the students was rather low (between 10 and 55%) for one thing, because of the difficulty in reaching them as they commonly attended lectures in widely separated localities in consequence of the universities having been bombed. Between 65 and 90% of the students were tuberculin positive.

German physicians and German personnel also participated in the work of vaccinating

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school children; by the beginning of 1949 a vaccination group as a rule consisted of only one Swedish physician or nurse and the rest Germans. The Swedish personnel had gradually been increased, in November comprising 21 individuals.

The vaccinating was started in the cities of the Ruhr district, since the overcrowding of living quarters in this bomb-damaged industrial area was extremely great. Other groups that to a lesser extent were vaccinated coincidentally with the school children were pupils in the trade schools, students, younger miners and industrial workers, and hospital personnel. When the vaccination of school children in a town was finished, the trained German personnel continued the vaccination of other groups of the population.

Each BCG program was carefully introduced by such means as articles in the daily press and posters in the streets. In vaccination of the school children, it appeared that lectures with a follow-up discussion with the teachers were of great importance. Approximately 60 to 70% of the school children received the permission of their parents to become BCG vaccinated. From September to December, the school children in the towns of Gelsenkirchen, Duisburg, Dortmund and Oberhausen, among others, were vaccinated. About 240,000 individuals were tuberculin tested and about 100,000 were vaccinated. From Jan. 17 to Feb. 28, the corresponding figures were 190,000 and 94,000, respectively. The vaccination of school children was then terminated in the cities of Essen and Düsseldorf.

Two tuberculin tests were performed, in order to sort out the tuberculin positive individuals. For children up to 16 years of age, there was first made a patch (plaster) test and then a Mantoux test with 0.5 mg. The patch test was made as follows: without previous cleansing, a dab of ointment was applied to the skin over the sternum and covered with adhesive tape, which was removed after an interval of two days. The reading was done after four days. This test was done throughout by the German dispensary nurses, commonly one week before the vaccination group began operations. The patch test was compulsory for all school children, while the Mantoux test was made only on those negative to the patch test, whose parents had given a written permission to the BCG vaccination. Some children, less than 1%, reported that they had had fever and a marked swelling of the arm subsequent to the injection. Neither temperature nor a generalized swelling of the arm remained, however, at the reading of the test, which was done after the interval of 72 hours. In no instance was there necrosis. Some of these marked reactions were due to the fact that a feeble positive reaction to the patch test was overlooked. It therefore seems to be without risk to proceed to such a comparatively heavy Mantoux dosage after the patch test. Individuals above 16 years of age were tested with two Mantoux tests, 0.05 and 0.5 mg.; the test was considered positive if a 6 mm. large infiltration remained after 72 hours. The individuals that were shown to be tuberculin negative to Mantoux 0.5 mg. were BCG vaccinated high up on the outer aspect of the left thigh, rather dorsally in order to avoid irritation from the child's garter. The vaccine used, as well as the tuberculin, was of Swedish make. The former was prepared by the bacteriologic laboratory of the Sahlgren Hospital in Gothenburg. The head of the laboratory, Dr. Wassén, has prepared the vaccine himself since 1926. The dosage employed was 0.05 mg. intracutaneously, the same dosage proposed by Wallgren[2] when he introduced in 1926 the intradermal method of vaccination. The vaccine was delivered weekly by air and was never more than two weeks old when used.

A vaccination group comprising two vaccinators and their personnel made, on the

average, 1,500 tests daily. About 4,500 school children who were negative to the patch test could accordingly be Mantoux tested and vaccinated per week.

The incidence of tuberculosis infection among the school children of the Ruhr towns, vaccinated to date, was fairly uniform, wherefore the values for Dortmund only, which with its 380,000 inhabitants is one of the largest cities in this district, are presented in Fig. 1 below. The tabulation is based on a series of 55,000 school children, 22,000 of whom were vaccinated. The number of participants was large (76%). It is found that among the children who recently had begun school, 26.4% were tuberculin positive and 49% of the children who finished school at 14 years of age were tuberculin positive.

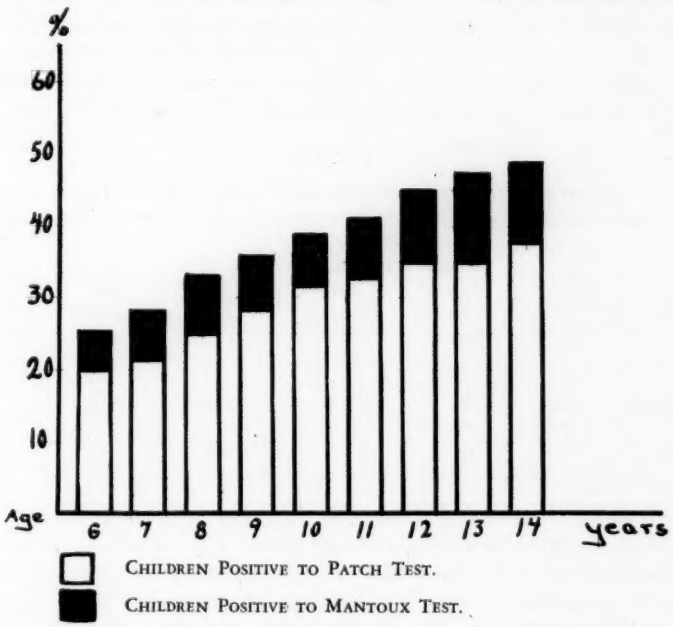

Fig. 1. Incidence of tuberculous infection among school children in Dortmund.

Because of the shortage of food prevalent until the summer of 1948, several German physicians feared that the BCG vaccination might have a different course than in Scandinavia. Some apprehended an increase of the virulence of the BCG vaccine in these often undernourished children with subsequent severe complications. Others did not expect the number of tuberculin positive individuals to be as great as was shown. In order to investigate these conditions the Swedish personnel made follow-up investigations on children in Gelsenkirchen and studied two German follow-up examinations from Duisburg and Oberhausen. The results of these three investigations are presented in Table I. In Sweden we usually perform a tuberculin test with Mantoux 1 mg. directly following vaccination, but according to the wish of the German physicians a patch test was first made and then a Mantoux test with 0.5 mg. We also tested 207 BCG vaccinated children who were negative to the patch test with Mantoux 1 mg. but did not obtain a higher percentage of

positive children with this greater dosage. Of these follow-up examinations, it is only the Gelsenkirchen series that has been tested with Mantoux also. We find here a tuberculin positivity in 92.8% of the BCG vaccinated children. This figure should be higher probably in the two German series, in which nearly all of the children had shown a local reaction to the vaccination, as against 9% of children with absence of local reaction in our series. Among these latter, only 68% were tuberculin positive, while 96% of those that showed a local reaction on vaccination were positive. It is known from experience that a number of patients do not become tuberculin positive notwithstanding a local reaction, although investigations by Törnell[3] and Ustvedt,[4] among others, indicate that there was a take also in these cases, which implies that the true figure for successful vaccinations is greater than indicated by the figures for tuberculin positivity. This seems to be about the same as is reported in BCG vaccinations in the Scandinavian countries.

In evaluation of the local reaction, one must take into consideration the interval between the vaccination and the follow-up examination. If it takes place as late as in these

TABLE I

FOLLOW-UP EXAMINATION OF BCG VACCINATED SCHOOL CHILDREN

	No. of School Children Followed Up	% with Absence of Local Reaction	% with Ulcers Larger Than 15 mm. in Diameter (10 mm. in Gelsenkirchen)	% Positive to Patch Test	% Patch and Mantoux Positive	Interval Between Vaccination and Follow-Up Examination in Wks.
Gelsenkirchen	9.295	9	0.3	70.0	92.8	13
Duisburg	17.225	0.04	0.5	83.0	—	15
Oberhausen	9.618	0	2.0	70.5	—	11

three investigations a number of the necroses following vaccination will have had time to heal. If, on the other hand, only the larger lesions which usually are slow in healing are reported, one should be able to draw certain comparisons with other series in which the follow-up examination is done after an interval of six to eight weeks. Malmros,[5] on the basis of his Swedish series, reports 1.6%, a figure equalled only by that from Oberhausen. Inquiries have also been made relevant to more serious complications, such as have called for hospitalization or surgery. In one case only has such a complication occurred, this in the form of an inguinal abscess that was drained surgically. The pus was sterile on culture. No report has as yet been received as to whether Myco. tuberculosis was demonstrated. From this investigation, accordingly, it does not seem as though there had been more marked reactions or more complications in these German children than in the Swedish children.

The Swedish BCG action in Germany has thus progressed as per schedule. Great interest has been shown by the German medical profession and by the population. This is shown best by the fact that the number of individuals requesting vaccination is on a steady increase, and also by the fact that such a large number of German physicians have been instructed during this period that it now merely is a question of time when the Swedish personnel will not be needed. Our BCG vaccination has shown also that when a country is threatened by tuberculosis in a fairly short time interest can be awakened for

the BCG vaccination among the physicians as well as in the general population, so that they subsequently continue the vaccination.

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Spanish Abstract

La Expedición BCG Sueca en Alemania

La acción BCG sueca en Alemania ha progresado según el programa. La profesión médica alemana y la población han mostrado gran interés. Esto se demuestra mejor por el hecho de que el número de individuos que piden vacuna va en aumento y también por el hecho de que un gran número de médicos alemanes han recibido instrucción durante este período y dentro de muy corto tiempo el personal sueco no se necesitará más. Nuestra vacuna BCG ha demostrado también que cuando un país está amenazado por la tuberculosis en un corto tiempo se puede despertar el interés por la vacuna BCG entre los médicos así como en el público en general, así es que ellos continuan subsecuentemente la vacuna.

Norrtulls Hospital

BCG VACCINATION IN SWEDEN

By JOHN LUNDQUIST, M.D.
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BCG VACCINATION has been carried out in Sweden to a great extent since about 1927. The honor for taking this initiative is due to Prof. Arvid Wallgren, who at that time inaugurated a systematic BCG vaccination of practically all tuberculosis threatened children placed under dispensary supervision in Gothenburg. Shortly afterwards, the Swedish National Association against Tuberculosis started the vaccination of tuberculosis threatened and other newborns in the northernmost provinces of this country, where the tuberculosis rate was especially high. This vaccination, organized on a large scale, was performed perorally, however, and practical reasons, such as the great distances and the lack of trained personnel, prevented a systematic tuberculin testing following vaccination; consequently, the result can not be assessed.

The interest in BCG vaccination in Sweden has gradually increased. This may be illustrated by some figures. On July 1, 1940, a law was passed calling for compulsory registration for parenteral Calmette vaccination (the peroral vaccination has since long been abandoned). In 1940, 4,251 vaccinations were reported; in 1941, 11,360; and in 1942, 30,638 vaccinations, the majority of these falling within age groups 0 to 5 and 10 to 15 years. In 1945, the procedure of registration was changed; registrations are now made at the respective central dispensaries rather than, as previously, at the Medical Board. There are no statistical reports on the registration since 1943, but it appears from the annual reports of the dispensaries that the number of vaccinations performed at these alone has been on the rise continuously:

1943	57,135	vaccinations
1944	84,032	"
1945	112,497	"
1946	119,385	"
1947	131,342	"
1948	173,533	"

In addition, a large number of vaccinations were performed on the nondispensary clientèle: infants, school children and adults in association with fluorographic group examinations. The total number of individuals in Sweden that have been vaccinated once may be assessed at about one million (total population 6.8 millions).

By the law passed in 1944 relevant to the Swedish public educational system, it is ruled, *inter alia,* that tuberculin-negative teachers should be advised to have BCG vaccination. All newly enrolled pupils in schools are to be tuberculin tested, those with a negative reaction being advised to have BCG vaccination. This vaccination, moreover, is performed to a large extent, often in 100% of the tuberculin negative individuals.

In certain professional groups, it is provisional for appointment that the individual be

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tuberculin positive (up to 1.0 mg. Mantoux); namely, the personnel at the State mental homes, hospitals and dental clinics, the pupils in the nursing schools, and also the medical students entering hospital service. In practice, this implies that BCG vaccination is obligatory for the tuberculin negative individuals in these groups. In sanatoria for pulmonary tuberculosis and other tuberculosis institutions, tuberculin positive personnel only is engaged.

The medical authorities of the Royal Medical Board and of the Military Forces have proposed that BCG vaccination be compulsory for all conscripts who have not shown a positive tuberculin reaction, but the proposal has not been accepted by the government. According to a law of 1945, however, it is incumbent on the district dispensaries to issue a written summons to all registrees for military service (which commences about one year later) to present themselves at the dispensary for tuberculin tests and an eventual BCG vaccination. In this way about one half of all conscripts are BCG vaccinated prior to military service. The tuberculin negative individuals are urged to undergo vaccination, with the result that the great majority become vaccinated.

The Swedish National Association against Tuberculosis has since 1942 furnished supplies to physicians and nurses for BCG vaccination and associated tuberculin tests, and these have been a marked stimulus towards an intensified vaccination procedure. To date, a total of 1,041,175 Swedish crowns has been disbursed for this purpose.

It has not been possible, unfortunately, throughout Sweden to combine the continuous fluorographic examination of the population introduced in 1946 with tuberculin tests and BCG vaccination. In limited areas, however, it has been feasible to combine the group examination with BCG vaccination. In the fluorographic examination of the population of the town Örebro, performed by Malmros and his co-workers, 46,048 out of 46,380 individuals examined were tuberculin tested and 8,569 were BCG vaccinated, only 5.7% of the tuberculin negative individuals having refused vaccination. The Swedish National Association against Tuberculosis has recently completed a second fluorographic examination of the population of the island Gotland (about 60,000 inhabitants), associated with tuberculin testing and BCG vaccination. Work on the same lines is at present being carried out in the northernmost provinces of Sweden. The results are as yet not available for publication but support from the population has been excellent.

SUMMARY

It may without exaggeration be said that BCG vaccination is popular among the Swedish population and there has been registered no reaction against it, similar to that resistance which occasionally is asserted against smallpox vaccination.

SPANISH ABSTRACT

La Vacuna BCG en Suecia

Se puede decir sin exageración que la vacuna BCG es popular entre la población sueca y no se ha registrado reacción contra ella similar a la resistencia que a veces se hace sentir contra la vacuna de viruelas.

Johannesplan 1

CONGENITAL TOXOPLASMOSIS

Clinical, Histopathologic and Parasitologic Observations During Life and at Post Mortem

By SVEN GARD, M.D., J. HENNING MAGNUSSON, M.D., F. WAHLGREN, M.D., AND GUNNAR GILLE, M.L.
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THE parasitologic confirmation of the clinical diagnosis of human toxoplasmosis has been made at post mortem, in the majority of cases, by means of histologic demonstration of Toxoplasma in brain sections. Only in a few cases has the infection been transmitted to animals. The first strain of human Toxoplasma was isolated by Wolf, Cowen and Paige[1] by inoculating various species of animals with an emulsion of brain tissue from a child who died with cerebral symptoms 31 days after birth. This strain was studied in detail by the same authors[2, 3] and by Sabin.[4] Three additional strains of human Toxoplasma were later isolated by inoculations with emulsions of brain tissue.[5-7] In a few cases, strains have been isolated from cerebrospinal fluid[5, 8-11] and blood[12] obtained during the life of the patient.

The object of the present paper is to report on a case of congenital toxoplasmosis, diagnosed clinically, in a child who died at the age of 43 days. It was possible to verify the clinical diagnosis at post mortem not only serelogically and microscopically but also by means of biologic identification of Toxoplasma. A number of experimental animals were inoculated with material taken from the patient in the course of the illness (cerebrospinal fluid and liver puncture) and immediately after death (from the brain, liver, spleen and muscles). A strain of Toxoplasma ("G.L.") was isolated and studied in detail.

CLINICAL OBSERVATIONS

Case G. L.—Mother was 20 yrs. of age, unmarried and a primipara. She was born and brought up on a farm but during the past 3 yrs. had worked as a waitress in Stockholm and had only occasionally visited her home. As a child, she had pertussis, rubella and rubeola and, in 1946, icterus. Otherwise, she, as well as her 10 siblings and the father of the child, had been healthy.

Pregnancy was at first normal and mother underwent regular examinations at an antenatal clinic. During the last 3 mos. of pregnancy, she frequently had colicky abdominal pain and, therefore, found it difficult to be fully active. Uncomplicated delivery occurred 6 wks. before term. The infant, a girl, weighed 3330 gm. at birth; length was 50 cm. Vitamin K 5 mg. was given by mouth immediately after birth. From birth she was lethargic and difficult to feed. Partly on these grounds and partly since the mother had fever, both remained in the maternity ward for 17 days. They were then sent to the home for mothers at which the mother had stayed during pregnancy. At this time, mother felt well, her temperature was normal, and she showed no signs of infection.

The child was consistently lethargic and often difficult to wake. It was only with the greatest difficulty that she could be made to take the required amount of breast milk. Feces were of normal color and fairly firm, urine was a dark brownish-yellow. When she was 25 days old, she had taken her feeding satisfactorily but was impossible to wake 4 hrs. later. She felt extremely cold to the touch and the rectal temperature could not be registered with an ordinary thermometer. Since it

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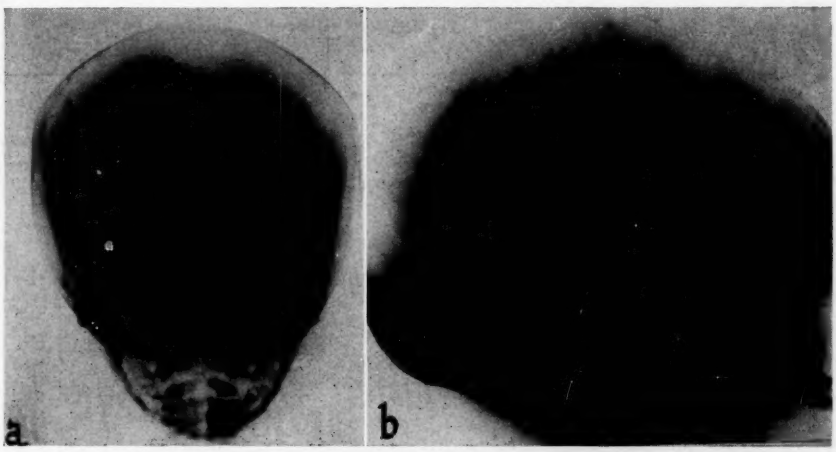
proved impossible to raise her temperature in the usual way with hot water bottles, the child was sent to the Sachs' Hospital for Children.

Patient was extremely lethargic on examination at this hospital. Body temperature was 33.8°C. She lay still and quiet during the entire examination and only on strong stimulation did she react with feeble cries and a few torpid movements. With the exception of moderate microphthalmia, she was well formed. Skin was pale, slightly cyanotic and markedly cold to the touch. Tonus and turgor were both decreased and there was some dehydration. Shape of the head was slightly hydrocephalic and was held in an opisthotonus position. Anterior fontanelle showed increased tension but was of normal width. No definite diastases of the sutures could be found. Neurologic examination revealed no further definite pathologic conditions. Heart: slow rhythm, otherwise normal. Lungs: normal. Skeleton: normal. No pathologic findings in the fauces or the oral cavity. Liver and spleen palpable



FIGS. 1a and 1b. Frontal and lateral roentgenograms showing wing-shaped calcifications situated symmetrically on either side of medial line in anterior part of cranial cavity.

slightly more than 2 finger-breadths below the costal margin. Lower margin of the liver felt firm. Roentgenologic examination showed considerable enlargement of both these organs.

Ophthalmologic examination showed the following: distinct microphthalmus. Shallow anterior chamber, bilateral aqueous flare, particularly on the right side, numerous synechiae (no reaction from the pupils); no red reflex on the right side, weakly reddish-grey on the left. Fundi not visible. Pressure was impossible to measure but appeared to be normal.

This finding of a bilateral uveitis of a secondary nature in conjunction with the previously mentioned symptoms made the clinical diagnosis of congenital toxoplasmosis probable.

Further and extremely strong support for this diagnosis was afforded by the roentgenologic examination of the skull, which revealed the following:

Upper part of the cranium of normal appearance and thickness, no diastases of the sutures. In the anterior part of the cranial cavity, as shown by Figures 1a and 1b, there were wing-shaped, slightly infiltrated calcifications, symmetrically situated on either side of the medial line.

The child died at the age of 43 days, having been in the hospital for the last 18 days of her life. During this period the following observations were made which threw further light on the clinical picture of the disease.

Body temperature fluctuated and showed considerable variations (33.8° to 40.8°C.) without any signs of infection in addition to toxoplasmosis. The details of the temperature curve are seen in Figure 2.

There were no cutaneous symptoms, such as exanthema, nor were any of the lymph nodes enlarged. The forementioned enlargement of the liver and spleen persisted and increased somewhat towards the end. Repeated neurologic examinations were made but it was extremely difficult to assess

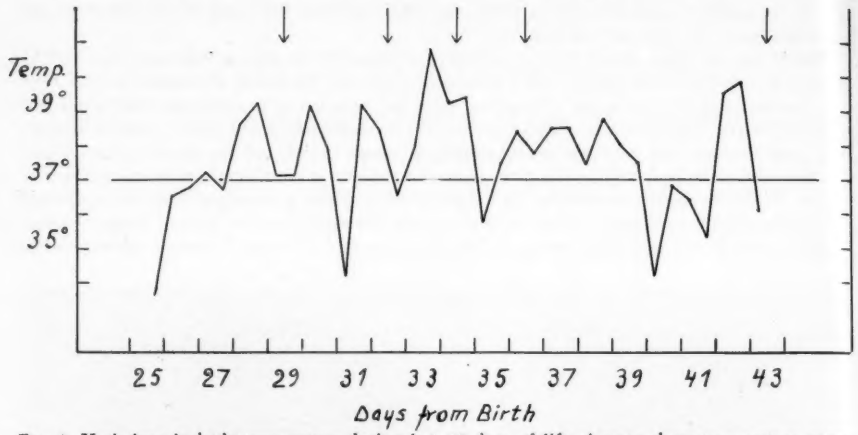


FIG. 2. Variations in body temperature during last 18 days of life. Arrows above temperature curve denote dates on which specimens were taken and inoculations made.

TABLE I

EXAMINATIONS OF CEREBROSPINAL FLUID

Age	Appearance of Fluid	Pressure cm. Water	No. of Cells/mm.³			Fluid Sugar	Protein						Culture of Fluid	Microscopic Examination of Dried Fluid	W.R., M.K.R.II. Kahn's R.
			Polymorphs	Mononuclears	Red Blood Cells		Pandy	None	Total Protein Concentration mg./100 cc.	Globulin Concentration mg./100 cc.	Albumin Concentration mg./100 cc.	Globulin-Albumin Ratio			
29 days (C.S.F.)	Clear, xanthochromic	8	28	70	18	39	+++ +	+++ +	377	106	271	0.39	No growth	Negative	Negative
32 days (ventricular fluid)	Clear, xanthochromic	—	130	360	—	—	+++ +	+++ +	—	—	—	—	No growth	—	—

TABLE II

BLOOD TESTS

Age	25 Days	26 Days	27 Days	28 Days	29 Days	30 Days	31 Days	32 Days	33 Days	35 Days	37 Days
Hemoglobin (%)	108										
Erythrocytes (milj.)	4.62										
Leukocytes	4,200		4,800	5,600	5,600	10,100	5,900	14,100	12,000		7,800
Nonsegmented (%)	18		7	4	17	10	9	5	12		9
Segmented (%)	19		25	14	25	21	3	16	35		10
Eosinophils (%)	16		11	11	8	11	22	11	13		15
	(670)		(530)	(620)	(450)	(1,110)	(1,300)	(1,550)	(1,560)		(1,170)
Basophils (%)				1					1		
Lymphocytes (%)	47		57	70	46	53	62	64	34		64
Monocytes (%)					4	5	3	4	5		2
S.R. (mm./hr.)	2										
Prothrombin index	15	96	113	109	92	100					
W.R., M.K.R.II., Kahn's R.										Negative	

the findings since the child was usually somnolent. The opisthotonus position became increasingly pronounced. Otherwise, however, the neurologic condition remained on the whole the same as on admission. No convulsions occurred. There was no rigidity of the neck and both Kernig's sign and Brudzinski's sign were negative. The reflexes varied but no definitely pathologic changes could be established. Examination of the cerebrospinal fluid showed pronounced xanthochromia, a considerable raised protein content, an increase in the number of cells, the presence of red blood corpuscles and a sub-normal sugar content (Table I).

As is shown by Table II, the patient on admission exhibited hypoprothrombinemia with an index of 15. Vitamin K 10 mg. was given by mouth and the prothrombin index remained subsequently within the normal limits.

Blood counts were made regularly and the results are assembled in Table II. They showed a

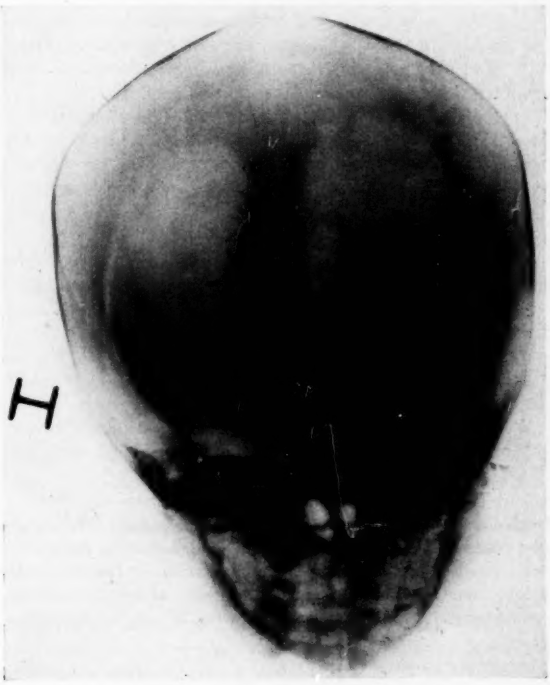


FIG. 3. Ventriculogram showing considerable hydrocephalus, mainly symmetric.

relatively high number of eosinophil granulocytes but otherwise nothing of note. Tuberculin tests yielded negative results, as did analyses of the urine and feces.

Ventricular puncture was made on the 36th day of life; 40 ml. of fluid were withdrawn and replaced with a corresponding quantity of air. Ventriculography revealed considerable hydrocephalus, which was mainly symmetric (Fig. 3). The bilateral intracranial calcifications appeared to be chiefly localized to the caudal part of the thalamic region and anteriorly in the base of the anterior horn of the lateral ventricle.

The disease progressed and the patient died. During the last few days, she was consistently deeply somnolent.

Diagnosis of congenital toxoplasmosis could be made with a great degree of certainty, as indicated previously, on the basis of the following clinical symptoms alone: (1) eye lesions in the form of distinct microphthalmia and chronic bilateral uveitis of a secondary nature; (2) considerable hydrocephalus internus, mainly symmetric; (3) cerebral calcifications.

In addition, there were further signs of injury to the central nervous system. Thus, at birth there was pronounced lethargy which became increasingly apparent and during the last days of life the infant was deeply somnolent. Convulsions, however, did not occur. It is possible that they would have occurred later had the patient survived. In 1 patient with congenital toxoplasmosis[13, 14] who is still alive and has been under regular observation since Sept. 1945, convulsions started only at the age of 1½ to 2 yrs. and then took the form of severe epileptic attacks. The findings in the cerebrospinal fluid in the case reported here also support the diagnosis of congenital toxoplasmosis.

The considerable enlargement of the liver and spleen found in this case can well be considered as associated with Toxoplasma infection, as can the hypoprothrombinemia. The last mentioned symptom, even in connection with hemorrhagic manifestations, was observed earlier in a patient suffering from congenital toxoplasmosis.[13, 15] It is remarkable that in the present case the hypoprothrombinemia persisted until the age of 25 days.

Another factor of interest is the marked and continuous eosinophilia with values considerably in excess of the normal upper limit. Thus, on the 32nd and 33rd days of life, the number of eosinophils exceeded 1500/cc. In a case of cogenital toxoplasmosis reported earlier,[13] eosinophilia was also present, but was more transient in nature and not so pronounced.

Owing to the illness of the child, her mother underwent a thorough examination in connection with the admission of the child to the hospital. The results were, however, negative. In her case, the infection had evidently taken place imperceptibly without giving rise to any noticeable clinical symptoms. Despite thorough investigations, it proved impossible to demonstrate the source of the infection.

Postmortem Findings

Anterior fontanelle fairly tense. Sutures no wider than normal but the bones of the cranium easily displaceable towards each other. Fairly abundant fresh hemorrhage between the dura and the cerebrum, particularly over the frontal lobes. Subarachnoid space filled with a fairly large quantity of clear yellowish fluid. Vessels engorged.

Dissection of the brain shows lateral ventricles to be extremely dilated but not the 3rd and 4th ventricles. Cerebral tissue around the ventricular system and particularly within the central ganglia shows a greyish-yellow discoloration and softening. Measurement in the section of the cortex of the hemispheres and the subcortical tissue is only 3 to maximally 8.10 mm. No macroscopic changes in the cerebellum, pons varolii or medulla oblongata, or in the spinal cord. Dural venous sinuses normal. Hypophysis cerebri of normal size, no changes visible.

Pericardium contains a small quantity of clear fluid. Heart dilated and flabby. No malformations. Valves normal. Myocardium pale reddish-brown. Aorta and pulmonary artery normal.

Lungs free in the pleural cavities which contain no fluid. Left lung parenchyma is pale, entirely air-filled and exudes a small quantity of clear, frothy fluid from the cut surface. In the upper region of the right lower lobe there are a number of greyish areas that are not air-filled. Remaining parts of lung show the usual extent of air-filled pale parenchyma. Mucosa of the trachea and bronchi pale with some frothy deposit.

Mucosa of the pharynx and esophagus pale grey.

No enlarged lymph nodes in the mediastinum. Thymus extremely reduced in size with a pale grey cut surface.

No free fluid in the abdominal cavity.

Mucosa of the stomach and intestines normal.

Liver somewhat enlarged with an even surface, and of a firmer consistency than usual. Cut surface dark greyish-brown, showing no pattern.

Bile ducts, pancreas and portal vein: normal.

Spleen moderately enlarged with normal firm consistency and dark red, even cut surface.

Adrenals, kidneys, urinary tract, genital organs: normal.

Microscopic Examination

Central nervous system.—Leptomeninges both of the brain and of the spinal cord considerably infiltrated with inflammatory cells, among which are numerous eosinophil leucocytes.

Cerebrum.—The tissue in the vicinity of the lateral ventricles is to a great extent completely necrotic. Remains of nuclei and numerous finely-grained calcium deposits in the necrotic areas. Outside this necrotic zone the tissue both of the hemispheres of the cerebrum and of the central ganglia shows more or less pronounced necrobiosis and is plentifully infiltrated with inflammatory

cells, mainly leukocytes, and fat-containing cells. There are scattered calcium deposits in these areas as well.

The injury to the tissue decreases in intensity peripherally and there appear to be no essential changes in the cortex.

Similar but somewhat less pronounced inflammatory changes, but no calcium deposits, in the vicinity of the 3rd and 4th ventricles.

Within the medullary zone of the cerebellum, the medulla oblongata, pons varolii and the grey and

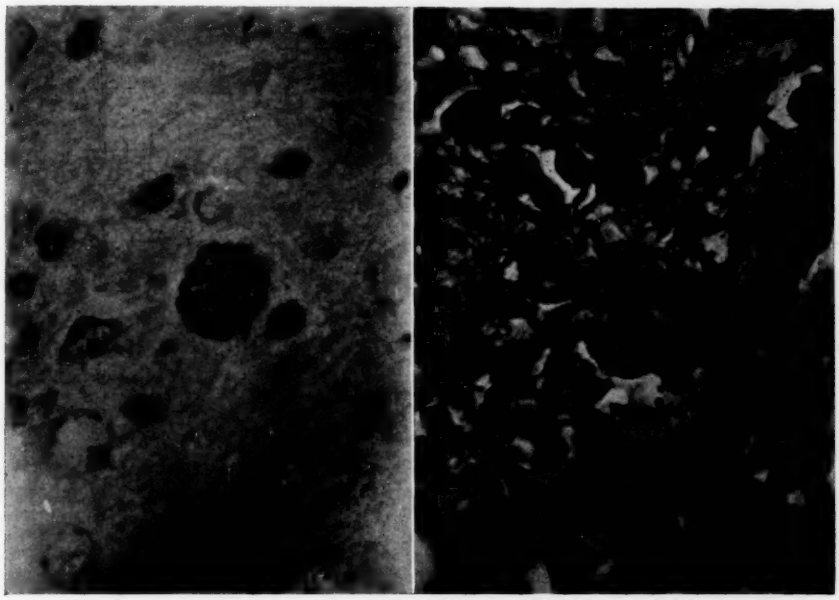


FIG. 4. Pseudocyst from affected areas in 1 hemisphere of brain. × 1350.

FIG. 5. Granulated cells in periportal tissue, probably mast cells simulating toxoplasmic pseudocysts. × 1350.

white tissue of the entire spinal cord are numerous small, irregularly rounded foci of granulomata, mainly consisting of histiocytes and occasional leukocytes. Occasional typical so-called pseudocysts can be demonstrated in the affected parts of the hemispheres of the cerebrum (Fig. 4). No free Toxoplasma can, however, be identified. On examination, the peripheral nerves show no pathologic changes.

The ocular bulbi were not examined.

Liver.—Lobular patterns somewhat blurred. No changes in the parenchymal cells. No necroses. The hepatic sinusoids are wide but contain only small quantities of red or white blood corpuscles. Many Kupffer's cells are swollen and contain iron pigment. The periportal mesenchymal tissue is more plentiful than normally, with swollen cells and sparse infiltration of lymphocytes. Scattered single pleomorphic cells rich in protoplasm, containing numerous round basophil granules. These cells distinctly resemble so-called pseudocysts. The granules are, however, smaller than the microorganisms in pseudocysts, and since they stain metachromatically with toluidine blue, these cells must be basophil leukocytes (mast cells).

Occasional bile canaliculi contain biliary thrombi.

No abnormalities in the large bile ducts or vessels (Fig. 5).

Spleen.—Follicles small and lacking germ centers. Splenic pulp is moderately engorged and contains a few eosinophil leukocytes. Sinus endothelial cells swollen, but no swelling of the pulp cells.

The sinus endothelial cells contain plentiful iron pigment.

The following organs were also examined but no changes of note found: stomach, small intestine, large intestine, pancreas, lungs, bronchi, kidneys, hypophysis cerebri, thyroid, adrenals, skeletal muscles.

The changes caused by Toxoplasma are thus mainly localized in the central nervous system. The picture, both macroscopically and microscopically, agrees in every respect with the conditions described in toxoplasmosis. The difficulties in demonstrating the micro-organisms are surprising in view of the widespread severe tissue injuries, but must be considered to depend on the fact that they cannot be identified among the remains of necrotic cells, calcium deposits, etc., except in the form of pseudocysts. No micro-organism could be detected in other organs although inoculation experiments demonstrated their presence in the liver and spleen.

As mentioned in the foregoing, occasional cells containing basophil granules are also found in the periportal tissue of the liver. They closely resemble pseudocysts although the granules are smaller in size.

As mentioned in the foregoing, occasional cells containing basophil granules are also found in the periportal tissue of the liver. They closely resemble pseudocysts although the granules are smaller in size.

The fact that the granules stain metachromatically with toluidine blue nevertheless reveals that these cells are basophil leukocytes (mast cells).

Isolation and Identification of Toxoplasma

Material was obtained for examination on five occasions. Cerebrospinal fluid was drawn by lumbar or ventricular puncture on the 4th, 7th and 11th day of admission, liver puncture was performed on the 9th day and finally brain, liver, spleen and pieces of the diaphragm were collected at autopsy. Spinal fluid and 10% organ suspensions were immediately inoculated intraperitoneally and intracerebrally in guinea pigs and mice. A number of the animals became ill in from 5 to 17 days after inoculation, with an average incubation period of 10 days. The symptoms were indicative of encephalitis, paralysis and convulsions being frequently observed.

Passages were regularly successful. After intracerebral inoculation in mice of brain or peritoneal exudate from sick animals, symptoms appeared on the 5th or 6th day and all animals were usually dead on the 7th day. After intraperitoneal injection ascites was evident on the 4th or 5th day. The survival time was 9 or 10 days.

Sections of brains were examined microscopically after formalin fixation and staining with hematoxylin-easin. As a constant feature, a heavy leptomeningeal infiltration was observed, most pronounced over the basal parts of the brain and in the interlobular areas. Numerous toxoplasma-like bodies were found, most constantly in the neighborhood of the ventricles.

The peritoneal exudate contained large numbers of typical Toxoplasma, easily discernible after vital staining with alkaline methylene blue.

Suspensions of the brains of sick animals were inoculated intracutaneously into normal rabbits and into one animal that had survived a previous inoculation with a strain of Toxoplasma of comparatively low virulence (LM). In the normal rabbits, there appeared at the site of inoculation an infiltration, reaching maximum size after about seven days, and developing an extensive central necrosis. About half of the animals died in 12 to 15 days. In the Toxoplasma-immune rabbit erythema and slight induration were observed two days after inoculation. The size of the lesion did not exceed one third of those observed in the normal animals and necrosis failed to appear. The animal survived.

The strain thus isolated (GL) has since then been maintained in intraperitoneal passages in mice and gradually gained in pathogenicity. The survival time after inoculation of 0.1 ml. of exudate is five to six days after 47 passages.

The compilation of data from the primary inoculations shown in Table III serves to indicate the most adequate procedure for the isolation of Toxoplasma.

Organs were ground without abrasive, made up to 10 to 20% suspensions with saline, and the coarse matter allowed to settle without centrifugation. Spinal fluid was inoculated undiluted. The amounts inoculated in guinea pigs were intraperitoneally 1.0 ml. and intracerebrally 0.1 ml., in mice 0.5 ml. and 0.025 ml., respectively.

TABLE III

RESULTS OF INFECTIVITY TESTS. ip = INTRAPERITONEAL, ic = INTRACEREBRAL INOCULATION. DENOMINATOR: NUMBER OF ANIMALS SUCCESSFULLY INOCULATED; NUMERATOR: NUMBER OF ANIMALS SHOWING TYPICAL SYMPTOMS

Date	Material Inoculated	Guinea Pigs		Mice		Result Recorded
		ip	ic	ip	ic	
May 7	C.S.F.			1/6	3/5	positive
10	"	0/6	2/4	0/6	10/14	"
12	Liver biopsy		1/3	0/3	0/6	"
14	C.S.F.	1/3	3/4	0/12	9/10	"
21	Brain			1/5	4/4	"
	Liver	0/1		0/4	0/4	negative
	Spleen			1/2	1/3	positive
	Diaphragm			0/4		negative

Six out of eight specimens tested yielded positive results. With these six specimens, 20 guinea pigs and 76 mice were successfully inoculated. The over-all attack rates were 35 and 39%, respectively. Intraperitoneal application gave 11% takes in guinea pigs, 9% in mice. For the intracerebral route the figures were 55 and 64%, respectively.

These figures indicate that guinea pigs and mice are about equally susceptible to human Toxoplasma and that, with due consideration to the amounts inoculated, the susceptibility to intracerebral inoculation was about 100 times greater than that to intraperitoneal application. This reasoning, of course, applies strictly to the particular strain encountered in the present case. Other human strains may show different affinities.

The results obtained with different materials are summarized as in Table IV, counting only intracerebral test inoculations.

Although these figures should be judged with caution, on account of the comparatively small number of animals inoculated, nevertheless they would seem to be significant in regard to the distribution of Toxoplasma in the tissues. Thus, they indicate a pronounced neurotropism of the parasite, in accordance with its behavior in experimental infections.

No blood or serum samples were tested for infectivity. However, considering the low infectivity of liver and spleen, *intra vitram* as well as postmortem, it may be assumed that only small numbers of Toxoplasma might have been found in the blood, which is the more likely since the serum was found to contain neutralizing antibodies. Therefore, in congenital toxoplasmosis with signs of cerebral involvement, cerebrospinal fluid is the material to be chosen in attempts at isolation of the etiologic agent, and intracerebral inoculation in mice or guinea pigs is to be preferred to other routes.

Particular interest seems to be attached to the positive result of the infectivity test performed on material obtained at liver puncture. Six mice and three guinea pigs were inoculated intracerebrally with this material and three additional mice intraperitoneally.

No other material was collected simultaneously and the animals were kept in isolation during the observation period. Contamination or laboratory infection can, therefore, be ruled out. One of the guinea pigs became paralyzed on the 10th day. It was killed on the 14th day and a strain of Toxoplasma was established by intracerebral passage of brain to mice. Accordingly, in obscure cases of enlargement of the liver, where congenital toxoplasmosis may be suspected, there seems to be a fair chance of verifying the suspicion by experimental inoculation of material obtained by liver puncture.

In a number of publications referred to in the foregoing, the results of infectivity tests were considered doubtful on account of the spontaneous occurrence of toxoplasmosis in the stock of experimental animals. Infections in rabbits with Encephalitozoon cuniculi seem to be fairly common in Sweden. Although we have not met with any active infections nor isolated any strains from rabbits in this laboratory during the last 10 years,

TABLE IV

Test Material	No. of Animals Inoculated	No. of Takes	Percentage
Brain	4	4	100
Cerebrospinal fluid	37	27	73
Spleen	3	1	33
Liver	13	1	8

toxoplasmosis has been observed in wild hares found dead,[16] and in serum neutralization tests on rabbits, carried out during the last two years. Roughly 3% of the animals showed complete immunity to the American Toxoplasma strains RH and LM, indicating infections in the past. In mice, imported from Denmark, and suffering from epizootic diarrhea, a protozoon was found in the epithelium of the distal part of the small intestine and the neighboring region of colon. It sometimes invaded the submucous tissue and, in a few cases, was found in the mesenteric lymph node and in the spleen. The nature of this protozoon was obscure at the time but certain facts point towards a diagnosis of Toxoplasma. No such observations have been made on our own breed of mice. Furthermore, among several thousand mice inoculated with Toxoplasma, not a single animal has shown any immunity. Our experience as to the frequency of spontaneous toxoplasmosis in the guinea pig stock is limited. So far, however, no animals tested have been immune and no spontaneous infections have been observed.

Against the background of this experience, and avoiding the use of rabbits in attempts to isolate Toxoplasma, we must consider a positive result of an infectivity test as practically 100% significant. The large number of takes in the present case can leave no doubt that the strain of Toxoplasma obtained originates from the sick child.

Serology

Blood samples were drawn from mother and child on the 7th day and from the mother again three weeks later. Neutralization tests were performed intracutaneously in rabbits. Serum from the mother neutralized completely 25 and almost 625 skin reactive doses of both strains tested (RH and LM). The serum of the child neutralized 5 but not 25 reactive doses.

A new *in vitro* technic for the measurement of Toxoplasma antibodies was given us by Dr. Albert Sabin in July 1948.[17] The method is based on the fact that Toxoplasma on

incubation with immune serum lose their ability to stain with methylene blue and other vital strains. The antibody responsible for this reaction is in itself thermostable. The reaction system, however, seems to be complex, the presence of a third factor, a "complement," being necessary. This factor is easily destroyed by heating to 56°C. or by standing at room temperature. It is present in normal human serum but seems to be lacking entirely or present only in small amounts in most animal sera. Consequently, the test is set up with a mixture of normal human serum and peritoneal exudate from mice as a source of Toxoplasma, to which is added varying amounts of test serum. After incubation at 37°C. for one hour the specimen is stained with alkaline methylene blue and examined microscopically. Stained and unstained extracellular Toxoplasma are counted and the serum titer is given as the highest dilution giving more than 50% unstained Toxoplasma. With proper controls, the method gives easily reproducible results.

The serum of the mother had been stored at −60°C. and titrations according to Sabin and Feldman were performed on Sept. 9, Oct. 1, Oct. 10 and again on Jan. 7. On all occasions both specimens showed identical titer values of 1:800 (final dilution 1:1600). Three different strains of Toxoplasma were used in the test: RH, LM and the one isolated from the child (GL).

In our experience with this test, comprising about 300 sera at the time of writing, titers of 1:400 or higher are obtained in cases with Toxoplasma infections in an active state or in recently subsided cases.

In an attempt to compare the strains GL, RH and LM immunologically, several sera of different titers were tested against all three strains. No immunologic differences were detected by this method.

Summary

An account is given of congenital toxoplasmosis in a child who died at the age of 43 days. The patient, who was somnolent from birth, showed the following symptoms: bilateral microphthalmia and chronic bilateral uveitis; considerable hydrocephalus internus, mainly symmetric, cerebral calcifications and pronounced typical changes in the cerebrospinal fluid, hypoprothrombinemia and eosinophilia; enlargement of the liver and spleen; marked lability of the body temperature with wide variations.

The postmortem findings, both macroscopic and microscopic, were typical in every respect, with pronounced necrotic encephalitis in the cerebrum and characteristic foci of granulomata in the brainstem and the spinal cord. Toxoplasma in the form of pseudocysts were demonstrated in the affected parts of the brain.

Typical Toxoplasma were isolated from the spinal fluid on three occasions, from material obtained by liver biopsy and from pieces of brain and spleen removed at autopsy.

Serum from the patient as well as from the mother gave a positive neutralization test in rabbits. The *in vitro* dye test according to Sabin and Feldman yielded a positive result with a high titer value.

The strain of Toxoplasma isolated ("G. L.") seems to be serologically identical with the American strains "RH" and "LM."

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SPANISH ABSTRACT

Toxoplasmosis Clínica: Observaciones Clínicas, Histopatológicas y Parasitológicas Durante la Vida y Después de la Muerte

Se da un relato de toxoplasmosis congénita en un niño que murió a la edad de 43 días. El paciente, quien desde su nacimiento estaba soñoliento, mostró los siguientes síntomas principales: microftalmía bilateral y uveitis bilateral crónica con catarata secundaria; considerable hidrocéfalo interno, generalmente simétrico, calcificaciones cerebrales y cambios típicos pronunciados en el flúido cerebro-espinal, hipoprotrombinemia y eosinofilia; ensanchamiento del hígado y del bazo; labilidad marcada de la temperatura del cuerpo con grandes variaciones.

Los descubrimientos después de la muerte, macroscópicos y microscópicos, fueron típicos en todo sentido, con encefalitis necrótica pronunciada en el cerebro y focus característicos de granulomata en la raíz del cerebro y la médula espinal. Toxoplasma en la forma de seudoquistes fueron demostrados en las partes afectadas del cerebro.

Los toxoplasmas típicos fueron aislados del flúido espinal en tres ocasiones, del material obtenido mediante la biopsia del hígado y de los pedazos de cerebro y bazo removidos en la autopsia.

El suero del paciente así como el de la madre dieron un ensayo de neutralización positivo en conejos. El ensayo de tinte *in vitro* según Sabin y Feldman dieron un resultado positivo con un alto valor de título.

La cepa de Toxoplasma aislados ("G.L.") parece ser serologicamente idéntica a las cepas americanas "RH" y "LM."

Sachs' Hospital for Children

COMPLEMENT FIXATION TEST IN TOXOPLASMOSIS AND PERSISTENCE OF THE ANTIBODY IN HUMAN BEINGS

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THE present investigation was undertaken to determine the possible usefulness of the complement fixation (CF) test in the diagnosis of human toxoplasmosis, with particular reference to the differentiation of active or recent infection from inactive, clinically unrecognized infections which may have occurred in the distant past. This differentiation is becoming increasingly necessary for the elucidation of the role of Toxoplasma in human disease, since the possibility exists that inapparent or clinically unrecognized infection with this protozoon parasite may be much more common than has been previously suspected. The first report on the CF reaction in toxoplasmic infection by Warren and Sabin[1] must now be regarded as inconclusive because a crudely prepared antigen of unknown potency was employed with a method (human and monkey sera were heated at 56° instead of 60° C. and the antigen-antibody-complement mixtures were incubated for only 30 minutes at 37° C.) which on the basis of present knowledge is obviously inadequate. Since that work was done, much has been learned about CF reactions with antigens prepared from virus-infected tissues and the "nonspecific" complement-binding constituents of normal tissues, which has a distinct bearing on the problem of preparing a specific CF antigen from infectious agents which can be propagated only in the tissues they parasitize.

Recently, Warren and Russ[2] reported the preparation of an antigen from the chorioallantoic membranes of embryonated chicken eggs experimentally infected with Toxoplasma, which was capable of revealing high titers of CF antibody in the sera of immune guinea pigs and of several human beings suspected of having been infected with Toxoplasma. The control antigen in these tests was an extract of chorioallantoic membranes from uninoculated embryonated eggs. They reported, however, that 4 of 11 "normal" sera (36%) and 3 of 14 sera (21%) with positive Wassermann reactions fixed complement at dilutions of 1:4 to 1:8 with both toxoplasmic and normal antigens, but they believed that these results were due to previous inoculation with vaccines of egg origin or to a syphilitic history.

Through the kindness of Dr. Joel Warren, these antigens became available to this laboratory for comparative tests on sera which were being studied for toxoplasmic antibodies by the recently developed dye test.[3] In tests on 66 human sera (heated at 60°C. for 20 min.) from individuals, suspected for 1 reason or another of possible toxoplasmic infection, there were 27 sera which fixed complement only with the toxoplasmic antigen, 33 which reacted neither with the toxoplasmic nor with the normal antigen and 6 (9%) which reacted in varying degree with both antigens. Neither previous inoculation with egg vaccine nor a syphilitic history were factors in the 9% of the sera which gave the troublesome nonspecific reaction. It is important to note here that these particular sera were not in themselves anticomplementary and that the antigens were complement-enhancing rather than anticomplementary. The antigens prepared by Warren and Russ[2] had been through only 1 cycle of low-speed centrifugation at 3500 r.p.m. for 15 min. on an angle machine, and following the observations of Kidd and Friedewald[4] and Havens et al.,[5] it appeared desirable to determine the effect

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TABLE I

EFFECT OF HIGH SPEED CENTRIFUGATION ON SUBSTANCE IN CHORIOALLANTOIC MEMBRANE ANTIGENS CAPABLE OF FIXING COMPLEMENT IN PRESENCE OF CERTAIN HUMAN SERA

Serum	Before Centrifugation at 13,000 r.p.m.								After Centrifugation at 13,000 r.p.m.								Saline + Serum 1:2
	Toxoplasmic Antigen + Serum 1:				Normal Antigen + Serum 1:				Toxoplasmic Antigen + Serum 1:				Normal Antigen + Serum 1:				
	2	4	8	16	2	4	8	16	2	4	8	16	2	4	8	16	
PRA	4*	3	1	0	4	2	0	0	trace	0	0	0	0	0	0	0	0
JOH	4	4	2	0	4	2	1	0	0	0	0	0	0	0	0	0	0

*Numerals refer to degree of fixation of 2 exact u. of complement—4=complete; 0=no fixation.

of further centrifugation at higher speed on the nonspecific component in the antigens prepared from the chorioallantoic membranes. Accordingly, both the toxoplasmic and normal antigens were submitted to an additional centrifugation at 13,000 r.p.m. for 1 hr. on a Swedish angle centrifuge (Sorvall—SS1) kept in a cold room at about 5°C. The results obtained with 2 sera shown in Table I indicate that this additional centrifugation was capable of removing the component in normal as well as toxoplasma-infected chorioallantoic membranes which fixed complement with certain human sera. Other tests indicated that the titer of specific CF antibodies in human sera which did not react with the original normal antigen was undiminished when they were tested with toxoplasmic antigen submitted to the additional centrifugation at high speed. On the other hand, the specific titer of human serum did diminish with the ultracentrifuged antigen when the original serum was also capable of reacting with the sedimentable component in normal chorioallantoic membrane. The results presented in Table II show that the actual potency of the antigen is not diminished by the additional centrifugation at 13,000 r.p.m., an observation also recorded by Warren and Russ.[2] It appeared, therefore, that the additional centrifugation at 13,000 r.p.m. for 1 hr. was capable of

TABLE II

EFFECT OF CENTRIFUGATION AT 13,000 R.P.M. FOR 1 HOUR ON POTENCY OF TOXOPLASMIC COMPLEMENT-FIXING ANTIGEN IN EXTRACTS OF CHORIOALLANTOIC MEMBRANES

Antigen 20% Suspension of Infected Chorioallantoic Membranes Centrifuged at 3,500 r.p.m. for 15 Min.		Fixation of 2 Exact u. of Complement in Presence of 32 u. of Antibody at Indicated Dilutions of Antigen	
		Before Centrifugation at 13,000 r.p.m.	After Centrifugation at 13,000 r.p.m.
No.	Dilution		
1 C	1:2	4*	4
	1:4	4	4
	1:8	4	4
	1:16	4−	3−
	1:32	0	0
	1:64	0	0
3 A	1:2	4	4
	1:4	4	4
	1:8	3−	2
	1:16	0	0

*4=complete; 0=no fixation.

improving the specificity of the toxoplasmic antigen prepared from infected chorioallantoic membranes without diminishing its potency. With this improved antigen, even a serum titer of 1:2 to 1:4 was significant and indicative of the presence of specific toxoplasmic CF antibody.

The early studies by Warren and Sabin[1] on brain and peritoneal exudate of toxoplasma-infected mice as a source of CF antigen yielded negative results because of inactivity of the brain extracts and the anticomplementary properties of the peritoneal exudate, although other factors relative to technic and potency of the antisera could have been responsible. It appeared desirable to reinvestigate these possible sources of antigen by more modern methods and to compare the results with those obtained by the use of chorioallantoic membranes. The chief technical problems in preparing a CF antigen from mouse brain (whether it be normal or infected) are: (1) removal of those components which are anticomplementary particularly when incubation for 16 to 24 hrs. in the cold is the method of choice, and (2) removal of those substances from normal as well as infected brain which react with certain normal or syphilitic human sera. Following the observations of Havens et al.,[5] and my own experience with various encephalitis viruses[6] and dengue,[7] the best way to remove the anticomplementary properties from brain suspensions is by high speed centrifugation. Since the resulting product, unlike that prepared from chorioallantoic membranes, is still capable of fixing complement in low dilutions with certain nonsyphilitic and syphilitic human sera, the best way to solve the 2nd problem is by benzene extraction. In the present study, 2 to 3 wk. old mice were inoculated intracerebrally with 0.03 cc. of mouse peritoneal exudate, obtained 3 days after intra-abdominal injection of exudate rich in the "RH" strain of Toxoplasma (over 400 consecutive mouse passages)[8] and diluted 1:2 with saline. The mice exhibited nervous signs and began to die 42 hrs. after inoculation; at 46 to 47 hrs. when additional mice began to die, all were killed with chloroform, exsanguinated by cutting across the chest, and the brains removed. Films of these brains, stained with Wright's stain, showed in each field large numbers of Toxoplasma, predominantly of the large, round variety which is found prior to binary fission.[9] Seventeen mouse brains, weighing 6.45 gm., were ground with enough saline (without abrasive) to yield a final volume of 32.2 cc. (20% suspension). This was put in a 250 cc. pyrex reagent bottle and quickly frozen in a thin layer on the sides of the bottle by rolling it in a solid CO_2-alcohol mixture; as soon as it was completely frozen, it was rapidly thawed in a water bath at 37°C. and the process was repeated 3 times. A single freezing and thawing suffices to kill the Toxoplasma and repetition of the process 3 times leaves almost all Toxoplasma intact, but the latter was done to make the procedure comparable to that employed for the chorioallantoic membranes. After 15 hrs. in an ordinary refrigerator, the frozen and thawed mixture was centrifuged at 13,000 r.p.m. for 30 min. in the cold room; the 22 cc. of clear supernatant liquid was again centrifuged at 13,000 r.p.m. for 1 hr. A small, translucent pellet was present and 21.7 cc. of supernatant liquid to which was added 0.22 cc. of 1% merthiolate (to yield a final concentration of 1:10,000) constituted the final antigen.

The antigens from peritoneal exudate were prepared as follows: Mice weighing approximately 20 gm. each received an intra-abdominal injection of 0.2 cc. of a freshly prepared 1:10 dilution of peritoneal exudate in saline. Four days later when most, although not all, of the mice exhibited distended abdomens, they were killed and the peritoneal exudate (average yield of 1 cc. per mouse), removed with a capillary pipette, had 19 million extracellular Toxoplasma per cc. Normal saline was then used (1 cc. per mouse) to wash out the abdominal cavities and these washings were found to contain 10 million Toxoplasma per cc. The original exudate and washings were pooled and centrifuged on a horizontal machine at 2,000 r.p.m. for 20 min., which sedimented cells and Toxoplasma. One antigen was then prepared from the supernatant liquid and another from the sediment. The supernatant liquid was centrifuged at 13,000 r.p.m. for 1 hr. in the cold room, and while there was no distinct pellet, the sides of the tube might have been slightly coated; the water-clear supernatant liquid plus merthiolate to a final concentration of 1:10,000 constituted 1 antigen. The sedimented cells and Toxoplasma representing 1% by volume of the centrifuged material (0.1 cc. sediment was obtained from each 10 cc. of the pool of exudate and saline washings) were taken up in 2 cc. of saline for each 0.1 cc. of sediment (1:20 by volume) and transferred to a Ten Broeck grinder in which a smooth suspension was prepared. The material was then washed out with an equal volume of saline yielding a final 2.5% (or 1:40) concentration of sedimented cells and Toxoplasma in saline. Microscopic examination of a drop of this suspension with the aid of alkaline methylene blue revealed almost equal masses of Toxoplasma and leukocytes. Eight cc. amounts were then placed in lusteroid tubes (100 mm. × 13 mm.) and rapidly frozen (solid CO_2 + alcohol) and thawed (water

bath at 37°C.) 10 times. A voluminous, flocculent precipitate appeared, and while microscopic examination of the material at the end of this process still revealed some intact Toxoplasma, it was evident that most of the Toxoplasma had disintegrated. After storage in an ordinary refrigerator for about 16 hrs., the flocculent precipitate was removed by horizontal centrifugation at 2,000 r.p.m. for 10 min., and the clear, supernatant liquid was further centrifuged at 13,000 r.p.m. for 1 hr. in the cold room. The water-clear supernatant liquid plus merthiolate in a final concentration of 1:10,000 constituted the antigen from the sedimented leukocytes and Toxoplasma.

The data presented in Table III show the comparative effect of the various preparations on the activity of complement under the conditions of the test requiring incubation in a refrigerator for

TABLE III

EFFECT OF VARIOUS ANTIGENS ON ACTIVITY OF COMPLEMENT

0.25 cc. of antigen and sufficient 0.85% NaCl to yield total volume of 1 cc. was added to indicated amounts of complement and mixtures left in refrigerator (5° C.) for 18 hrs. 0.5 cc. of mixture of equal parts of 3% washed sheep erythrocytes and diluted hemolysin (3 u./0.25 cc.) was then added and the whole put in water bath at 37° C. for 30 min. Final reading made after cells settled in refrigerator.

Antigen Added to Complement		Degree of Hemolysis at Indicated Amounts (cc.) of 1:50 Dilution of Guinea Pig Complement								No. of Exact u./0.5 cc.
		0.5	0.4	0.3	0.25	0.2	0.15	0.10	0	
None—saline control		4*	4	3	2	trace	0	0	0	1.25
Normal CAM†—20%		4	4	4	4	3.5	2	1	0	2.00
Toxoplasma CAM—20%		4	4	4	4	3.5	2.5	1	0	2.00
Toxoplasma CAM—10%		4	4	4	4	3.5	2.5	1	0	2.00
Toxoplasma CAM— 5%		4	4	4	4	3.5	2	1	0	2.00
Toxoplasma mouse brain		4	4	4	4	3.5	2	1	0	2.00
Mouse peritoneal exudate freed of cells and Toxoplasma by centrifugation	Undil.	0	0	0	0	0	0	0	0	<1.00
	1:2	0	0	0	0	0	0	0	0	<1.00
	1:4	1	trace	0	0	0	0	0	0	<1.00
	1:8	2	1	trace	0	0	0	0	0	<1.00
	1:16	4	4	2.5	1.5	trace	0	0	0	1.25
Extr. of Toxoplasma and cells (2.5% by vol.) centrifuged from mouse peritoneal exudate	Undil.	4—	3.5	2	1	0	0	0	0	<1.00
	1:2	4	4—	2.5	1.5	trace	0	0	0	1.00
	1:4	4	4	3.5	2.5	.1	0	0	0	1.25

* 4 = complete, 0 = no hemolysis.

† CAM = chorioallantoic membrane.

approximately 18 hrs. It may be seen that the chorioallantoic membrane and mouse brain preparations all enhanced the activity of complement to such an extent that 1 exact unit was contained in 0.25 cc. of the 1:50 dilution of complement in the presence of the antigens as compared with 0.4 cc. for the exact unit in the saline titration.* This means that if 0.8 cc. of the 1:50 dilutions of complement were selected as representing 2 exact units on the basis of the saline titration (as has

* The term "enhancement" rather than "protection" is used here because it was found that the complement in saline does not lose potency under the conditions of this experiment; it appears rather that the addition of various tissue extracts or heated sera which are themselves devoid of complementary activity are capable of "enhancing" the activity of complement in the manner shown

been recommended for some viral CF tests[11]), it would actually contain (0.8/0.25) 3.2 exact units on the basis of the titration in the presence of antigen. Tests have shown that the use of the larger amount of complement can give a 4-fold reduction in the titer of a serum and a 2- to 4-fold reduction in the titer of antigen. In contradistinction to the complement-enhancing properties of the chorioallantoic membrane and properly centrifuged mouse brain preparations (normal as well as infected), the antigens prepared in a similar manner from mouse peritoneal exudate were highly anticomplementary and centrifugation for an additional hr. at 13,000 r.p.m. had no effect on this property. The antigen from the supernatant liquid of the peritoneal exudate had to be diluted 1:16 and that from the sedimented Toxoplasma and leukocytes had to be diluted 1:4 to eliminate the anticomplementary activity. It should be noted, however, that even after centrifugation at 13,000 r.p.m. for 2 hrs., the preparations from mouse brain or peritoneal exudate (the latter used in a concentration devoid of anticomplementary activity) were capable of fixing complement "non-specifically" with those few human sera which reacted with the normal chorioallantoic membrane antigen before but not after centrifugation at 13,000 r.p.m. for 1 hr. (as shown in Table II).

TABLE IV

COMPARISON OF VARIOUS TYPES OF TOXOPLASMIC COMPLEMENT-FIXING ANTIGENS

Infected Material Used for Preparation of Antigen	Concentration of Infected Material in Original Preparation	No. of u. of Antigen in Processed Original Preparation	Lowest Dilution of Processed Preparation Free of Anti-complementary Properties	Yield of Antigen per Egg or Mouse	
				Original Processed Preparation	After Dilution to Contain 4 u./0.25 cc.
Chorioallantoic membranes	20%	8–16	Undiluted	12 cc.	24–48 cc.
Allantoic fluid	100%	<1	Undiluted	—	—
Mouse brain	20%	8	Undiluted	1.3 cc.	2.6 cc.
Mouse peritoneal exudate freed of Toxoplasma and cells by centrifugation	50%	64	1:16	2 cc.	32 cc.
Toxoplasma and cells centrifuged from mouse peritoneal exudate	2.5%	16	1:4	0.8 cc.	3.2 cc.

Tests for antigenic potency in the presence of 16 to 32 units of antibody indicated (a) that there was as much specific toxoplasmic CF antigen in mouse brain as in the chorioallantoic membranes; (b) that the toxoplasmic and cell-free liquid portion of the mouse peritoneal exudate contains more antigen per unit volume than the extracts of mouse brain or chorioallantoic membranes; (c) that the antigenic potency of the centrifuged extract of the 10 times frozen and thawed, sedimented Toxoplasma and leukocytes cannot be accounted for on the basis of the associated liquid exudate. If the disrupted Toxoplasma contributed nothing to the potency of the antigen, the maximum number of units (per 0.25 cc.) that one would have expected in the extract would have been 1.6 (64 units divided by 40 which is the dilution by volume of the sedimented Toxoplasma and cells in the extract) and 16 units were actually present. A comparison of the properties of the various antigens (summarized in Table IV) indicates that with the exception of the allantoic fluid of infected embryonated eggs which was practically devoid of toxoplasmic antigen, all the other preparations could be used in tests requiring 4 units of antigen. However, it is clear that the yield from 1 egg is at least 10 times as great as from 1 mouse brain. Although the yield of antigen from the liquid portion of the peritoneal exudate from 1 mouse is in the same range of magnitude as that derived from the chorioallantoic membrane of 1 egg, there are the following disadvantages to the use of peritoneal exudate in routine tests for toxoplasmic CF antibodies: (a) the 4 units of

in Table III. It is regrettable that no tests were made to determine whether or not this enhancement was due to the Mg^{++} and Ca^{++} contained in the tissue extracts and sera as suggested by Mayer, Osler, Bier and Heidelberger.[10]

antigen are contained in a dilution which is just barely free of anticomplementary properties; (b) if the amount of complement used is determined by its potency in the presence of the antigen it would vary with the dilution of the test serum which is complement-enhancing in the lower but not the higher dilutions (it is possible, however, that this objection might be overcome by using saline with added Mg^{++} and Ca^{++}, as suggested by Mayer, Osler, Bier and Heidelberger[10]); (c) there is no good, comparable, normal control antigen, and (d) centrifugation at high speed does not eliminate the component which fixes complement "nonspecifically" with certain human sera. For

TABLE V

PERSISTENCE OF COMPLEMENT-FIXING ANTIBODY IN CHILDREN WITH CLINICALLY RECOGNIZED CONGENITAL TOXOPLASMOSIS AND IN MOTHERS WITHOUT RECOGNIZED SIGNS OF INFECTION EXCEPT FOR HAVING GIVEN BIRTH TO INFECTED CHILDREN

Children with Congenital Toxoplasmosis				Mothers of Children with Proved Infection			
No.	Name	Age	C-F Titer	No.	Name	Time Since Delivery	C-F Titer
1	GLO	5 wks.	0	1	GLO	5 wks.	1:32
2	CON	10 "	1:32	2	CON	10 "	1:32
	"	18 "	1:32		"	18 "	1:16
3	HAW	6 mos.	1:32	3	HAW	6 mos.	1:16
4	COD	9 "	1:16	4	COD	9 "	1:4
5	OLI	14 "	1:32				
6	McC	15 "	1:32	5	McC	15 "	1:16
7	JOH	15 "	1:128+?	6	JOH	15 "	1:32
8	BON	15 "	1:2	7	BON	24 "	1:4
	"	30 "	1:2		"	30 "	1:4
9	WOE	3½ yrs.	1:8	8	WOE	3½ yrs.	1:8
10	WRI	3⅔ "	1:16	9	WRI	3⅔ "	1:4
11	HEM	5 "	1:16	10	HEM	5 "	1:16
12	KOP	6 "	1:8	11	KOP	6 "	1:8
13	HEL	6½ "	1:16	12	HEL	6½ "	1:32
14	HOO	7 "	0				
15	BLA	7½ "	1:2				
16	AUG	11 "	1:4	13	AUG	11 "	1:8
				14	TAY	6 wks.	1:64
					"	4 yrs.	1:8
				15	RAI	9 mos.	1:32
					"	18 "	1:16
				16	F-47	8 "	1:32
				17	F-45	3 yrs.	1:64

these reasons, it would appear that the antigen of choice is that prepared from toxoplasma-infected chorioallantoic membranes according to the method of Warren and Russ[2] plus the additional centrifugation at 13,000 r.p.m. for 1 hr., as suggested by the present studies, for the purpose of removing the "nonspecific" component which fixes complement with certain human sera.

The method used in the tests now to be reported (and recommended for routine purposes) is as follows: The toxoplasmic antigen prepared from chorioallantoic membranes (and preserved in the lyophilized or frozen states, or stored in the fluid state in an ordinary refrigerator for not longer than 2 wks.) was titrated for antigenic potency against 16 to 32 units of antibody (the results with smaller amounts of antibody varied with different sera) and used in a dilution which contained 4 units of antigen per 0.25 cc. This was done once for each new lot and was not repeated except after long periods of storage. Both the toxoplasmic and normal antigens were found to be complement-enhancing. However, since the extent of enhancement occasionally varied with different lots of sensitized erythrocytes, a preliminary titration of the complement to be used

in the test in the presence of the diluted antigen was carried out according to the procedure, shown in Table III, but without overnight incubation and with the sensitized erythrocytes which were to be used the following day for the test itself. When the titer of the frozen or lyophilized lot of complement in saline and the enhancing activity of the antigens were known, a 4-tube test was sufficient to indicate the dilution of complement to be used in a test on any given day, to contain 2 exact units in the presence of the antigen. It is possible that by using saline with added Mg^{++} and Ca^{++} in all parts of the test as suggested by Mayer, Osler, Bier and Heidelberger[10] the titer of complement in saline and in the presence of complement-enhancing antigen might prove to be the same, but this was not done in the present work. The sera were diluted 1:2 with saline and heated at 60° C. for 20 min. Further 2-fold dilutions were prepared in the tubes to be used in the test (changing pipettes frequently when the dilutions were carried beyond 1:16) the amount of diluted serum remaining in the tube being 0.25 cc. After 0.5 cc. of the predetermined dilution of guinea pig serum containing 2 exact units of complement had been added, 0.25 cc. of antigen was added to all the tubes except 1 in each series which contained the lowest dilution of the serum used in the test and received 0.25 cc. of saline instead of antigen (this was the anticomplementary control for the serum). The diluted complement used in the test was again titrated in the presence of antigen and along with all the other mixtures was left in a refrigerator (at about 5° C.) for 16 to 24 hrs. The sensitized sheep erythrocytes (from blood stored in Alsever's solution) representing a mixture of equal parts of a 5% suspension of washed cells and hemolysin diluted to contain 3 u./0.25 cc. were prepared in sufficient quantity to be used both for the preliminary titration of complement and for the test itself the next day, and were stored in the refrigerator when not in use. The sensitized sheep cells were added in 0.5 cc. amounts to all tubes, which were then incubated in a water bath at 37° C. for 30 min. The results were read immediately but the final estimate of varying degrees of hemolysis or fixation was made after the red cells had settled in the refrigerator. The titers or endpoints recorded in Table V represent the original dilutions of the sera (before addition of complement, antigen and sensitized red cells) which gave 2-plus or better fixation (approximately 50% or less hemolysis) with the toxoplasmic antigen and none at all (i.e., in the lowest dilution of serum used which as a rule was 1:2) with the normal antigen.

The data presented in Table V provide a basis for estimating the persistence of toxoplasmic CF antibodies in human beings who suffered either from the clinically apparent disease or from the clinically unrecognized or inapparent infection. Of the 16 children, aged 5 wks. to 11 yrs., all presented signs previously reported[9] as occurring in congenital toxoplasmosis, and all had neutralizing antibody for Toxoplasma demonstrable by the dye test.[9] Some lived in different parts of the U.S.A. and others in England (Nos. 4, 6 and 10) or Holland (No. 8).* Of the 17 individuals with inapparent or unrecognized infection listed in Table V, 13 were mothers of living children with congenital toxoplasmosis studied simultaneously, and 4 (Nos. 14-17) were mothers of children who died of congenital toxoplasmosis confirmed by postmortem demonstration of Toxoplasma in their tissues. These mothers gave either no history of illness of any kind during the pregnancy under consideration or suffered from symptoms whose relationship to the toxoplasmic infection must at least remain doubtful or unproved. It is known that at least 7 of the mothers (Nos. 6, 7, 9, 10, 11, 12 and 15) in this group gave birth to subsequent children who were entirely normal, suggesting that the original infection with Toxoplasma had either been eradicated or localized to a point where further congenital transmission of the infection would not occur. In the light of this information it is noteworthy that CF antibodies in titers of 1:4 to 1:64 for the toxoplasmic antigen (with completely negative results for the normal control antigen) were found in the serum of each of the 17 mothers obtained at intervals of 5 wks. to 11 yrs. after pregnancy. While the higher titers of 1:16 or over predominate (10 of 11) during the first 2 yrs., 3 of 10 sera obtained at later intervals also had high titers (1 serum of 1:64 at 3 yrs., 1 of 1:16 at 5 yrs., and 1 of 1:32 at 6½ yrs.). The tendency for the titers to drop with time is suggested by the tests on serial

* For material and information relative to the individuals listed in Table V, acknowledgment is made to Drs. S. Van Creveld of Amsterdam, Holland; C. A. St. Hill and H. G. Farquhar of Liverpool, England; C. B. Beattie, Sheffield, England; M. Bruce, Syracuse, N.Y.; A. T. Bunts, Cleveland, Ohio; C. P. DeFuccio, Jersey City, N.J.; S. Farber and C. A. Janeway, Boston, Mass.; R. B. Lawson, Winston-Salem, N.C.; R. V. Platou and M. E. Wegman, New Orleans, La.; D. F. Sullivan, Mobile, Ala.; J. Warren, Washington, D.C.; P. Wasserman, Cincinnati, Ohio; C. W. Woodruff, Nashville, Tenn., and W. W. Zuelzer, Detroit, Mich.

specimens obtained from mothers Nos. 2 and 15, and especially so after an interval of approximately 4 yrs. in mother No. 14. Since there is some evidence to suggest that inapparent infection with Toxoplasma may not be uncommon after the 20th yr. of life,[12] it is of interest that CF tests on the sera of 20 mothers who gave birth to children with neurologic or ocular disturbances or both not due to toxoplasmosis (as judged by the fact that the sera of the children had neither neutralizing [dye test] nor CF antibodies) yielded 4 positive results (20%) with titers of 1:2, 1:2, 1:8 and 1:16 (Table VI).

An analysis of the results obtained with the sera of the children suffering from congenital toxoplasmosis again indicates a predominance (7 of 9) of higher titers of 1:16 or over during the first 2 yrs. of life; however, 3 of 9 patients over 2 yrs. of age had titers of 1:16 at 3⅔, 5 and 6½ yrs., respectively. Analysis of the data relative to the children with the negative or low titers provides information of particular interest. The negative CF reaction with the serum of 5 wk. old patient

TABLE VI

SUMMARY OF RESULTS OF TOXOPLASMIC COMPLEMENT FIXATION TESTS ON SERA OF MOTHERS AND CHILDREN WITH CONGENITAL OCULAR AND/OR NEUROLOGIC DISTURBANCES OF TOXOPLASMIC AND NONTOXOPLASMIC ETIOLOGY

Group	No. Tested	Positive		C-F Titers at Indicated Age or Time after Delivery	
		No.	%	0–23 Mos.	2 Yrs. or Over
Children with congenital toxoplasmosis	16	14	87.5	128, 32, 32, 32, 32, 16, 2, 0	16, 16, 16, 8, 8, 4, 2, 0
Children with congenital ocular and/or neurologic disturbances not due to toxoplasmosis	24	0	0	—	—
Mothers of children with congenital toxoplasmosis	17	17	100	64, 32, 32, 32, 32, 32, 16, 16, 4	64, 32, 16, 8, 8, 8, 4, 4
Mothers of children with congenital disturbances not due to toxoplasmosis	20	4	20	16, 8, 2, 2, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	0

No. 1 was obtained in repeated tests in which the serum of the patient's mother yielded titers of 1:32. This result was incompatible with our findings on the fate of placentally transmitted maternal antibody in normal children[13] according to which one would have expected a titer in the range of 1:8 to 1:16 at 5 wks. after birth. It was of interest, however, that the titer of neutralizing antibodies (dye test) was as high (1:4,096) in the serum of this child as in that of its mother, and that titers of this magnitude have been found only in individuals (human beings and animals) with relatively recent toxoplasmic infection.[3] It is, furthermore, of interest that this child exhibited clinical evidence of an acute infection, compatible with toxoplasmosis, and died 3 days after the serum was obtained. Studies which we have carried out on guinea pigs and a rhesus monkey experimentally infected with Toxoplasma indicated that the neutralizing antibodies (dye test) appeared early during the period of active infection reaching peak titers of 1:1,024 to 1:4,096 at 2 to 3 wks. while the CF antibodies were not detectable during that period and made their 1st appearance at a later date.[14] It would appear, therefore, that a negative test for CF antibodies associated with a high (1:256 or more) dye test titer for neutralizing antibodies may under certain circumstances be taken as a serologic index of active infection. In patient No. 8,[15] the CF titer of 1:2 at 15 mos. of age was associated with a dye test titer of 1:1,024 for neutralizing antibodies; since repetition of these tests on serum obtained 15 mos. later yielded the same results, there is at least an equal possibility that the low titer of CF antibody could be due either to poor initial response or to a subsiding infection. The negative test for CF antibody in the 7 yr. old patient No. 14 (presenting chorioretinitis, cerebral calcification, epileptic seizures and mental retardation) was associated with a dye test titer of 1:16 and a strong, specific skin reaction to toxoplasmic antigen (1:100 and 1:1,000). Although the patient's mother had died before the present study, the clinical and serologic data are compatible with a diagnosis of congenital toxoplasmosis, and the absence of CF

antibodies can probably be correlated with the 7 yr. interval since the infection. The 7½ yr. old patient No. 15 presenting the complete clinical tetrad of congenital toxoplasmosis (hydrocephalus, cerebral calcification, chorioretinitis and psychomotor retardation) had been observed by me since 6 mos. of age when the diagnosis was first made by serologic tests on the serum of the mother and the patient.[9] Here, again, the partial complement fixation obtained at a serum dilution of 1:2 was associated with a dye test titer of 1:16 and several attempts since 6 mos. of age to demonstrate Toxoplasma in the cerebrospinal fluid and cerebral cortex (obtained by biopsy) were negative. Recently this patient died of an intercurrent infection and an attempt to demonstrate Toxoplasma in his brain again yielded negative results. The conclusion is perhaps warranted here that the antibodies diminish in titer in a subsided toxoplasmic infection. It is, furthermore, noteworthy that not a single positive CF test was obtained with the sera of 24 children, aged 4 mos. to 5 yrs., with congenital ocular and neurologic disturbances not due to toxoplasmosis as judged by the complete absence of neutralizing antibodies in their sera according to the dye test (Table VI).

Discussion

Elimination from the chorioallantoic membrane antigens of a nonspecific component capable of fixing complement with certain normal human sera has yielded a toxoplasmic CF test of such specificity that even serum titers of 1:2 to 1:4 could be regarded as significant. Using the improved antigen, not a single instance was encountered in which a positive CF test (titer of 1:2 or more) was not associated with the presence of neutralizing antibody for Toxoplasma. However, since toxoplasmic neutralizing antibody (dye test or rabbit test) can be present in either high or low titer in the absence of CF antibody, it is apparent that in human beings as in animals these antibodies appear and disappear at different times after onset of infection. The present study has shown that toxoplasmic CF antibodies can persist for at least six years, and in some individuals even longer, after clinically recognized as well as after inapparent or clinically unrecognized infections. Since the individuals with the inapparent or clinically unrecognized infections investigated in this study were mothers who had given birth to children with proved congenital toxoplasmosis, there can be no question of the toxoplasmic infection in them. Furthermore, since at least seven of these mothers subsequently had given birth to normal children, at a time when the toxoplasmic CF antibody titers in some of their sera were still high (32, 32, 32, 16, 8, 4, 4), it is clear that this antibody can persist in individuals in whom the infection has been either eradicated or suppressed sufficiently to prevent its congenital transmission. The present data also suggest that a high titer of neutralizing antibody (dye test titer of 1:256 or more) associated with a completely negative test for CF antibodies may be indicative of a recently acquired, active infection. On the other hand, a low titer of neutralizing antibodies (dye test titer of 1:64 or less) under similar circumstances (except perhaps during the first week of infection) would be indicative of a subsided toxoplasmic infection of many years' standing or conceivably of an infection with another agent possessing a common antigen with Toxoplasma; no such agent, however, has as yet been found. It is also apparent that the CF test, using the improved antigen from infected chorioallantoic membranes and the standardized procedure here described, can be a valuable aid in the diagnosis of toxoplasmosis. In most instances of congenital toxoplasmosis, especially during the first six years of life, the CF test on the serum of the child and mother can by itself provide the serologic confirmation of the diagnosis.

Summary

An antigen prepared from toxoplasma-infected chorioallantoic membranes, improved by centrifugation at 13,000 r.p.m. for one hour which removed a nonspecific component capable of fixing complement with certain normal sera, proved to be the preparation of choice for toxoplasmic CF tests. Though it was possible to prepare an antigen of similar

potency from mouse brain, the yield from one egg is at least 10 times more than from one mouse. The peritoneal exudate of mice freed of Toxoplasma and cells contains eight times as much antigen per unit volume as a 20% extract of mouse brain or chorioallantoic membranes, but its anticomplementary properties, which cannot be removed by high speed centrifugation, can be eliminated only by extensive dilution. The highly centrifuged and diluted peritoneal exudate, however, still contains a component which fixes complement with certain normal human sera. Sixteen children, aged 5 weeks to 11 years, with clinically recognized congenital toxoplasmosis and 17 mothers, with inapparent or clinically unrecognized infection except for having given birth to children with proved toxoplasmosis, were investigated for the presence and persistence of CF antibodies. With the improved antigen and the standardized method that was used, even titers of 1:2 and 1:4 were significant and invariably associated with toxoplasmic neutralizing antibody. The sera of all 17 mothers gave positive CF tests with titers ranging from 1:4 to 1:64, the higher titers predominating during the first two years after the delivery of the infected child. The sera of 14 of the 16 children (87.5%) with clinical evidence of congenital toxoplasmosis, confirmed by neutralization tests, gave positive CF tests with titers ranging from 1:2 to 1:128, the higher titers again predominating during the first two years after birth. One of the negative results, in a 5 week old child with active infection who died three days after the serum was obtained, was associated with a high (1:4,096) dye test titer for neutralizing antibody in its own serum, and a similar dye test titer (1:4,096) and a CF titer of 1:32 in the serum of its mother. The other negative result, in a 7 year old child with a dye test titer of 1:16, is believed to represent an instance of disappearance of CF antibody after an interval of seven years. Not one serum obtained from 24 children with congenital ocular or neurologic disturbances or both, not due to toxoplasmosis, gave a positive CF test with the toxoplasmic antigen; however, among 20 of their mothers, there were four sera with titers of 1:2, 1:2, 1:8 and 1:16. Toxoplasmic CF antibody can persist for at least six years, and in some instances even longer, in individuals with clinically recognized as well as inapparent or clinically unrecognized infections. Since at least seven of the mothers, who gave birth to children with congenital toxoplasmosis, subsequently gave birth to normal children at a time when the CF antibody titers in some of them were still high (32, 32, 32, 16, 8, 4, 4), it is clear that this antibody can persist in individuals in whom the infection has been eradicated or suppressed sufficiently to prevent its congenital transmission.

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SPANISH ABSTRACT

Ensayo de Fijación de Complemento en la Toxoplasmosis y Persistencia del Anticuerpo en Seres Humanos

Un antígeno preparado de membranas corioalantoicas infectadas de toxoplasma, mejorado mediante centrifugación a 13,000 r.p.m. por una hora, lo que removió un componente no específico capaz de fijar complemento con ciertos sueros normales, resultó ser la preparación escogida para los ensayos CF toxoplásticos. Aunque era posible preparar un antígeno de similar potencia del cerebro del ratón, el resultado de un huevo es por lo menos 10 veces más que el de un ratón. El exudado peritoneal de ratones libres de Toxoplasma y células contiene ocho veces tanto antígeno por volumen de unidad como un extracto de cerebro de ratón de 20% o membranas corioalantoicas; pero sus propiedades anticomplementarias, que no se pueden remover por medio de centrifugación de alta velocidad, pueden ser eliminadas solamente por medio de dilución. El exudado peritoneal altamente centrifugado y diluído, sin embargo, aún contiene un componente que fija complemento con ciertos sueros humanos normales. Dieciseis niños, de 5 semanas a 11 años de edad, con toxoplasmosis congénica clinicamente reconocida, y 17 madres, sin infección aparente o clinicamente reconocida, excepto por haber dado a luz a niños con toxoplasmosis probada, fueron investigados para la presencia y persistencia de anticuerpos CF. Con el antígeno mejorado y el método uniformado que se usó, aún títulos de 1:2 y 1:4 fueron significativos e invariablemente asociados con anticuerpos neutralizantes toxoplásmicos. Los sueros de todas las 17 madres dieron ensayos CF positivos con títulos de 1:4 a 1:64, los títulos más altos predominaron durante los dos primeros años después de dar luz al niño infectado. Los sueros de 14 de los 16 niños (87.5%) con prueba clínica de toxoplasmosis congénita, confirmada por ensayos de neutralización, dieron ensayos CF positivos con títulos de 1:2 a 1:128, de nuevo los títulos más altos predominaron durante los dos primeros años después del parto. Uno de los resultados negativos en un niño de 5 semanas de edad con infección activa que murió tres días después de que se obtuvo el suero, fué asociado con un alto título de ensayo de tinte (1:4096) para neutralizer el anticuerpo en su propio suero, y un título de ensayo de tinte similar (1:4096) y un título CF de 1:32 en el suero de su madre. El otro resultado negativo en un niño de 7 años con un título de ensayo de tinte de 1:16 se cree que representa un caso de desaparición del anticuerpo CF después de un intervalo de siete años. Ningún suero obtenido de 24 niños con desordenes oculares congénitos o neurológicos, o ambos, que no fueran debidos a toxoplasmosis, dió un ensayo CF positivo con el antígeno toxoplásmico; sin embargo, entre 20 de sus madres, hubieron cuatro sueros con títulos 1:2, 1:2, 1:8 y 1:16. El anticuerpo CF toxoplásmico puede persistir por lo menos seis años, y en algunos casos aún más tiempo, en individuos con infecciones clinicamente reconocidas lo mismo que con las que no son aparentes. Como por lo menos siete de las madres que dieron a luz niños con toxoplasmosis congénita, subsecuentemente dieron a luz niños normales en un tiempo cuando los títulos de anticuerpo CF en algunas de ellas estaban todavía altos (32, 32, 32, 16, 8. 4. 4), es claro que este anticuerpo puede persistir en individuos cuya infección ha sido destruída o suficientemente suprimida para evitar la transmisión congénita.

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HOSPITAL FATALITY RATES FOR PREMATURE INFANTS

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THE Study of Child Health Services (1945-1948), conducted jointly by the American Academy of Pediatrics and the Children's Bureau and the Public Health Service of the Federal Security Agency, was designed primarily to determine the amount and kind of medical care and health services children in the United States are receiving. Along with this main objective went certain supplementary studies that were expected to yield additional useful information without adding too greatly to the total effort expended. One of these side studies, the incidence of breast feeding in hospitals, has been reported.[1] The present paper deals with another of these by-products of the total study, namely, how many infants are born prematurely and what happens to them. It is only fair to say that the question was included not only to get facts, but also to indicate to persons in charge of nurseries for newborn infants the type of information that they should have about their hospital service.

Information is badly needed on the incidence of prematurity. The statement is frequently made that 5 to 6% of all live born infants are prematurely born, the percentage for the nonwhite group being somewhat higher. Since birth weight, the only reliable criterion for classification, has not in the past been required on the birth certificate except in a few places, the evidence supporting these figures is not complete for the country. It seemed desirable, therefore, to gather data on incidence among hospitalized births, because the study would cover all sections of the country, and all kinds of hospitals—large and small, public and private, teaching and nonteaching.

Not only do we lack knowledge of how many babies are born prematurely, but we do not have good information on how many of those born prematurely live. Census figures give the number of deaths for which prematurity is designated as the cause. Some deaths of premature infants are assigned to causes other than prematurity, such as congenital anomaly, birth injury or pneumonia. Were prematurity when it occurred always entered on the death certificate of infants we should still be unable to arrive at a picture of outcome for prematurity because the group at risk, namely, the total population of premature infants, is unknown. The Academy study, therefore, undertook to procure some information for the country from hospitals where birth weight is recorded and where one can presumably obtain a true fatality rate. For the purposes of this study, the term fatality is used to mean the deaths of premature infants occurring during the time the infants were premature.

For this section of the study, hospitals were asked to supply certain data on premature infants only if they cared for 50 or more per year. It seemed not worth while to collect information on premature infants from hospitals caring for only a few such

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infants. Of 808 hospitals* that might be expected to have 50 or more premature infants per year, about half (390)† supplied some information on the question. The 600,000 births that made up the sample are a little more than one half of the births occurring in the 808 hospitals eligible for this study.‡ The distribution by regions is not so good as one would wish, the South being considerably less well represented than other areas (Table I). From 10 states there were no reports, but these were mostly states with a small population or with few or no eligible hospitals.§ Coverage, therefore, might be called good, though far from complete.

The schedule used in the Study for recording hospital data provided for the reporting of number of live births in the hospital, and of number of cases and number of deaths for (a) premature infants born in the hospital in each of the following weight groups: (1) 1,000 gm. or less, (2) 1,001 to 1,500 gm., (3) 1,501 to 2,000 gm., and (4) 2,001

TABLE I

HOSPITALS REPORTING ON QUESTIONS RELATING TO PREMATURE INFANTS BORN IN HOSPITAL, BY REGIONS IN UNITED STATES

Region	Eligible Hospitals		Reporting Hospitals		Coverage by Reporting Hospitals	
	Number of Hospitals	Number of Births	Number of Hospitals	Number of Births	Per Cent of Hospitals	Per Cent of Births
United States, total	808	1,181,978	390	613,331	48.3%	51.9%
Northeast and Central	512	764,215	274	442,886	53.5	58.0
Mountain and Plain	66	83,739	31	36,328	47.0	43.4
Pacific	80	125,275	36	61,755	45.0	49.3
Southeast	107	139,841	36	51,285	33.6	36.7
Southwest	43	68,908	13	21,077	30.2	30.6

to 2,500 gm., and for (b) premature infants born outside and admitted. Material such as this, gathered from many different hospitals, by many different people, from records kept in a variety of ways, inevitably has many flaws. Some of these defects were readily apparent from the filled schedules. For example, notes in the margin might indicate that stillbirths were included with the count of live born premature infants; or more infants might be listed in the lowest weight group, an obvious inconsistency if all infants under 2,500 gm. were classified as premature births; or out of 21 infants under 1,000 gm., 20 might be recorded as surviving. To take care of these errors in the collection and reporting of data by the hospitals, rigid editing rules were established, the application of which reduced the material in amount but strengthened its validity.

* These hospitals had at least 800 births in a year, the number estimated to be required to yield a premature population of 50.

† All 390 did not report on all parts of the questions. See number indicated on each table.

‡ The reports covered a 12 month period. Most of the material was for 1946, but some was for 1945 and some for 1947.

§ Florida, Nevada, New Hampshire, New Mexico, North Dakota, Oklahoma, South Dakota, Vermont, West Virginia and Wyoming.

Incidence of Prematurity

The incidence of prematurity in this series, classifying as premature all live born infants weighing 2,500 gm. or less, was 6.1%. This group includes both white and non-white infants and the proportion of each is unknown. It has been shown by many investigations that race is one of the factors influencing birth weight.[2, 3] Data on non-white from a limited number of hospitals are given later in this paper. New York City's total incidence figures taken from birth certificates run somewhat higher than those in this study—7.3% in 1939[3] and 8.3% in 1946.[4] For the Chicago Lying-In Hospital for a five year period, 1941 to 1946, the incidence is 6.2%.[5]

Table II shows the percentage distribution in the different weight groups. Compared with New York City's figures for 1939 and 1946, the Academy Study showed fewer in the upper weight group (63% as compared to 69 and 72). It was our impression that

TABLE II

Incidence of Prematurity Among Infants Born in Hospitals*

Weight Groups	Number	Per Cent of Total Births	Per Cent of Total Prematures
Premature			
1,000 gm. or less	1,281	0.4	6.8
1,001–1,500 gm.	1,869	0.6	9.9
1,501–2,000 gm.	3,823	1.2	20.2
2,001–2,500 gm.	11,922	3.9	63.1
	18,895	6.1	100.0
Full term			
2,500 gm. or over	289,592	93.9	—
Total	308,487	100.0	—

* 193 hospitals reporting.

we may not have had complete reporting in this group. Regionally our figures show a higher incidence of prematurity in the South, probably a reflection of the number of Negro births.

Fatality Rate

The over-all fatality rate for premature infants born in 323 hospitals based on a total of over 32,000 such infants was 21.5%. This represents, it is believed, what happened to all infants weighing 2,500 gm. or less born in these hospitals and is a true fatality rate. This is assuming, of course, that discharge from the hospital represents the end of the stage of prematurity for the infant. The New York City rate which includes deaths during the first year of life was 18.4% for 1939 and 15.1% for 1946. It should be remembered that the New York groups had a larger percentage of babies in the upper weight group whose mortality rate is normally low. The Chicago Lying-In Hospital figure is 18.2, but represents only deaths in the first 10 days of life.

For infants born outside the hospital and admitted later the fatality rate was considerably higher—36.6% (based on 235 hospitals reporting about 2,000 cases). There are no data for this group by weight groups, so comparisons with those born in the hospital should be made cautiously. However, it is to be expected that this group would have a

larger proportion of deaths, for it is the normal practice to take into a premature center small babies or those doing badly. Figures on a group of premature infants admitted to hospitals for care are interesting and of value to the hospital in reviewing and appraising its own records, but do not reflect what happens to premature infants in general.

Survival of premature infants is known to be closely correlated with birth weight. This inverse relationship is demonstrated in Table III. As shown previously (Table II), more than 80% of premature infants are in the weight group 1,501 to 2,500 gm., where the chance of survival is fairly good. The small premature infants are relatively few in number, but even some of these do live. This study records for a one year period 220 infants weighing 1,000 gm. or less at birth who survived.

TABLE III

FATALITY RATE AMONG PREMATURE INFANTS BORN IN HOSPITAL, BY WEIGHT GROUP*

Weight Group	Cases	Deaths	Fatality Rate
			(per cent)
1,000 gm. or less	2,116	1,896	89.6
1,001–1,500 gm.	3,185	1,734	54.4
1,501–2,000 gm.	6,333	1,446	22.8
2,001–2,500 gm.†	13,960	1,020	7.3

* 277 hospitals reporting.

† Excludes 67 hospitals where count of premature infants in this weight group was less than twice that of preceding group.

NONWHITE PREMATURE INFANTS

Throughout the Academy Study it was difficult to obtain data on nonwhite children separately from white children. In a great many hospitals, even in areas where patients are segregated, records are not kept by race or color. It seemed unfair to compare rates from institutions accepting only white patients with those institutions accepting only

TABLE IV

INCIDENCE OF PREMATURITY AMONG INFANTS BORN IN HOSPITAL, BY RACE*

Weight Group	White		Per Cent of Premature Infants	Nonwhite		Per Cent of Premature Infants
	Number	Per Cent of Total		Number	Per Cent of Total	
Premature						
1,000 gm. or less	110	0.4	7.5	93	0.8	8.4
1,001–1,500 gm.	147	0.6	10.0	115	1.0	10.4
1,501–2,000 gm.	292	1.1	19.8	237	2.0	21.5
2,001–2,500 gm.	926	3.5	62.8	658	5.7	59.7
	1,475	5.6	100.0	1,103	9.5	100.0
Full term						
2,500 or more	24,885	94.4		10,540	90.5	
Total	26,360	100.0		11,643	100.0	

* Based on 22 hospitals that admitted both races and reported data separately by race.

Negroes. Out of the 323 hospitals, 65 furnished some data by race, but only 22 gave both births and deaths by weight groups. Using the same criterion for classification for white and nonwhite, namely, birth weight of 2,500 gm. or less, 5.6% of the white infants were premature as contrasted with 9.5% of the nonwhite infants (Table IV). The New York City figures (1939) are 7.0% and 11.7%, respectively.

Not only are a larger proportion of nonwhite infants premature but the fatality rate is greater (Table V). One would expect this difference because of the greater number of small babies in the nonwhite group. Differences in fatality rates, weight group by weight group, were, however, unexpected and are unexplained. Other studies have shown that groups of white and of nonwhite infants of the same sex and having the same birth weight have similar mortality rates.[6, 7]

TABLE V

FATALITY RATE AMONG PREMATURE INFANTS, BY RACE

	Fatality Rate (Per Cent)	
	White	Nonwhite
Premature infants born in hospital*	24.5	27.7
By birth weight†		
1,000 gm. or less	93.4	95.0
1,001–1,500 gm.	58.8	67.0
1,501–2,000 gm.	25.3	28.4
2,001–2,500 gm.	10.3	8.3
Premature infants born outside and admitted to hospital*	31.5	43.9

* 49 hospitals reporting.
† 55 hospitals reporting.

DISCUSSION

This material, though not as complete as one would wish, does reaffirm some impressions and adds to our knowledge some facts that are usable in planning programs of premature care. The reliability of the incidence figure of 6% for the country as a whole has been strengthened. There is confirmation of previous studies showing the higher incidence of low birth weight infants among the nonwhite group, a fact which needs to be borne in mind when making plans to cover a mixed group. It has been suggested that the criterion of a birth weight of 2,500 gm. or under is not valid for the Negro group, on the grounds that Negro infants are smaller than white infants at birth. Brown, Lyon and Anderson[8] suggest using a birth weight of 2,350 gm. for the Negro group, as comparable with that of 2,500 gm. for the white infants. Technically they may be correct and the difference in birth weight may be a racial one. It is well known, however, that the Negro group has a higher percentage of low income families, living in poor quarters and often with inadequate diet and medical care. Until a good series is obtained of Negro infants in a good environment and from families with a good income to compare with the low income group, the true significance of birth weight for the Negro will not be determined. The point, however, is academic. From the standpoint of care, which is the determining factor in favor of the 2,500 gm. level, the Negro infant

should be considered premature on the same basis as the white infant. The Negro fatality rate, though in this series not in excess of white for this weight group, 2,001 to 2,500 gm., is nevertheless 8.3%, indicating the need for special care.

An over-all fatality rate of 21.5% probably has more meaning for general use than rates we have had in the past coming from individual hospitals or from limited areas. It should be emphasized that the material came from existing records, not those designed to yield desired data, and that small hospitals having few prematures individually, though perhaps many collectively, are excluded. It should also be clear that the rates are based on an indefinite period of life. Survival at time of discharge from the hospital was asked, not to the age of 10 days, one month or a year.

This material emphasizes anew that comparisons of figures from different series are valid only if the composition of the groups by weight is known.

The real significance of this material is the highlighting of what we do not know and what steps can be taken to gather the facts. The first step has been taken in the revision of the Standard Certificate of Live Birth to include weight at birth as an essential item. It will be a long time before all registrars are getting this information completely. A second step is the improvement of hospital records, so that they are complete and uniform enough for collective use. During the course of this study we were told repeatedly by hospital administrators that they would be glad to keep records in a form usable by survey or planning groups provided they were given guidance and the methods were simple. The Children's Bureau has produced a form for recording statistics of premature births that would facilitate uniformity and would be useful to the hospitals as well.

Finally, this material points to the need for gathering more comprehensive data from hospitals on what happens to premature infants in order to have a better base line for measuring improvement in care. Could a study be made of a sample of hospitals representing all sizes and kinds, answers could be secured to such questions as: Does a series of premature centers in a state to which infants are transported reduce mortality significantly? Do small infants born in small hospitals have a better chance of survival if transported? Are we reducing mortality in some weight groups and not in others? Such a study would not only answer questions, but would be an educational force for improving hospital care to premature infants.

Conclusions

Data are presented from about half of the hospitals in the United States caring for 50 or more premature infants a year. In these hospitals there were about 600,000 births during 1946.

The incidence of prematurity, using as the definition of a premature infant one that was born alive weighing 2,500 gm. or less, was 6.1%. For white infants it was 5.6% and for nonwhite 9.5%.

The fatality rate for the group born in the hospital was 21.5% and for those born outside, 36.6%.

The close relation between survival and weight at birth is shown.

For nonwhite infants the fatality rate was higher than for white infants—27.7% for the group born in the hospital and as contrasted with 24.5, and 43.9 for those born outside as contrasted with 31.5.

There is need for better hospital records and for more comprehensive data on survival among premature infants.

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Spanish Abstract

Proporciones de Fatalidad de Hospital para Infantes Prematuros

Como una parte del Estudio Pediátrico de la Academia de los Servicios de la Salud del Niño, se obtuvo información de hospitales que tenían a su cuidado 50 o más infantes prematuros sobre el número de partos vivos y sobre casos y muertes de niños prematuros nacidos en el hospital y nacidos fuera y admitidos para su cuidado. En los hospitales elegibles que dieron información (casi la mitad del total), cerca de 600,000 nacimientos tuvieron lugar en un año. La incidencia de nacimientos antes de tiempo en estos hospitales, clasificando como prematuros todos los infantes que nacieron vivos pesando 2,500 gm. o menos, fué de 6.1%.

De una muestra pequeña, donde se dió la raza, la incidencia para infantes blancos fué 5.6% y 9.5% para los que no eran blancos. La proporción de fatalidad, es decir, la muerte antes de que salieran del hospital, fué 21.5% para el grupo de los nacidos en el hospital. Para aquellos que nacieron afuera del hospital y fueron admitidos para su cuidado, la proporción fué 36.6. Se muestra la estrecha relación entre la supervivencia y el peso en el parto. La proporción de fatalidad en los niños que no eran blancos fué más alta que para los niños blancos. Para el grupo nacido en el hospital, la proporción fué 27.7 para los que no eran blancos en contraste con 24.5 para blancos, y los que nacieron fuera 43.9 en contraste con 31.5.

Children's Bureau, Washington, D.C.

MECHANISM OF EMERGENCE OF RESISTANCE TO STREPTOMYCIN OF H. PERTUSSIS AND H. PARAPERTUSSIS DURING TREATMENT WITH THIS ANTIBIOTIC

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IT IS now recognized that streptomycin fails to cure infections caused by a number of different gram negative bacilli[1-7] which initially show *in vitro* sensitivity; the infection improves at first both clinically and bacteriologically but soon becomes worse and coincidentally the infecting organism exhibits a high degree of resistance. The cells responsible for the phenomenon of emergence of resistance to streptomycin in H. influenzae infections[8] and in those due to five enteric gram negative bacilli[9, 10] have been demonstrated to arise as the result of bacterial mutation and are therefore independent of the action of the antibiotic. Streptomycin exerts only a selective action; its rapid lethal effect on the sensitive members permits the minute number of resistant mutants, present initially in all large bacterial populations, eventually to make up most or all of the population. The limitation of the therapeutic action of a number of antibacterial agents as a result of this phenomenon has been reviewed.[11]

In an effort to predict the importance of emergence of resistance of H. pertussis and H. parapertussis during streptomycin therapy, these species were studied for evidence of highly resistant cells in large bacterial populations and to determine whether the resistant members exhibit traits characteristic of mutants.

This paper presents evidence that the variants of H. pertussis and H. parapertussis which are resistant to streptomycin also arise as a result of bacterial mutation. A preliminary report has been made.[9, 10] The resistant organisms have been examined for evidence of the following traits characteristic of mutants:

1. Demonstration of their independence of the action of streptomycin by showing their continuous irregular occurrence with different prevalence in independent cultures of same population size and strain.

2. Transmission of resistance unchanged in degree through many subcultures in the absence of streptomycin.

3. A low rate of occurrence of the resistant variants, not varying significantly among different strains of the same species.

MATERIAL AND METHODS

Examination for Trait 1:—Each of these organisms was examined by the following procedures to determine whether its variants resistant to 1000 mcg. of streptomycin per cc. exhibit Trait 1. All strains* studied were cultivated from patients with pertussis; they were maintained in a desiccated

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* Five different strains of H. pertussis were used in these investigations, 3 cultivated from patients treated at Babies Hospital and 2 from patients studied by Dr. Pearl Kendrick. Of the 5 strains of H. parapertussis used, 2 originated from patients studied at Babies Hospital and 3 were isolated by Dr. Kendrick.

state on filter paper under high vacuum.[12] For each *in vitro* test a dried culture was used; 0.2 cc. of broth was added to the tube and after thorough mixing with the culture on filter paper, the suspension was seeded on the surface of a Bordet-Gengou plate. A 48 hr. incubation period is needed to obtain good growth from the dried state; the entire growth is transferred by means of a platinum loop to 0.5 cc. of broth. The resulting heavy suspension is used to inoculate a Bordet-Gengou plate, which yields a good growth within 24 hrs.; it is removed by washing with 3.5 cc. of broth. The resulting suspension is seeded in 0.5 cc. amounts on Bordet-Gengou agar in 5 petri dishes. The yield from these 5 plates after a 24 hr. growth period is harvested in 65 cc. of broth and used as the inoculum in 0.5 cc. quantities to produce multiple (20 for H. pertussis and 10 for H. parapertussis) independent cultures on the surface of Bordet-Gengou agar in petri dishes. The prevalence of resistant organisms in the inoculum used for producing independent cultures was determined by seeding 2 cc. into each of 25 pour plate preparations of Bordet-Gengou medium containing streptomycin. The 5 plate source of this inoculum increases the possibility of seeding resistant cells on some of the 10 or 20 independent cultures which in turn increases the chance of greater irregularity of distribution of resistant colonies. The multiple independent cultures were incubated 30 hrs. for H. pertussis and 18 hrs. for H. parapertussis and the growth on each plate was removed by washing with a constant volume of broth, 3.5 cc., and transferred to an individual tube. From each 1 of the latter suspensions in tubes, after thorough mixing, 1 cc. was pipetted to an empty sterile petri dish and 1.2 cc. to a flask to form a pool which after further mixing was seeded in 1 cc. quantities to each of a series of 10 petri dishes. This provided 2 series of plates containing approximately the same number of organisms; in 1 series each plate received its inoculum from a different independent culture; in the other, each plate was seeded from the same source, the pool. Melted and cooled Bordet-Gengou agar containing appropriate concentrations of streptomycin was added to the plates holding each of the 1 cc. suspensions of the 2 series and was thoroughly mixed; after an incubation period of 6 days colony counts were recorded. Colonies in the agar medium can be detected by the surrounding zone of hemolysis.

Throughout this study all streptomycin medium used for studying H. pertussis variants contained 100 mcg./cc., and for H. parapertussis, streptomycin 1000 mcg./cc. Preliminary studies had demonstrated that all H. pertussis colonies which formed in 100 mcg./cc. were also resistant to 1000 mcg./cc. Tests carried out in duplicate, using each of these concentrations of streptomycin, showed no significant difference between the number of colonies of H. pertussis which grew in 100 and 1000 mcg./cc. Therefore streptomycin 100 mcg./cc. was adopted as the concentration for determining the presence of highly resistant variants of H. pertussis in order to conserve the antibiotic. With H. parapertussis, the situation was different: the frequency of variants which resisted the action of 100 mcg./cc. was 100 times as great as that of variants capable of growing in 1000 mcg./cc.

The results of these experiments will be described later.

Examination for Trait 2:—To determine whether the trait of resistance to high concentrations of streptomycin is an inherited characteristic, 2 colonies of H. pertussis and 2 of H. parapertussis which formed in agar containing high concentrations of streptomycin were subcultured 20 times in the absence of streptomycin at 24 to 48 hr. intervals. The colony selected for study in each instance was suspended in 0.1 cc. of broth and a 2 mm. loopful was seeded on the surface of 2 Bordet-Gengou agar plates, 1 containing the antibiotic. After 1, 10 and 20 subcultures of the descendents of these colonies, in the absence of streptomycin, the proportion of the population resistant to a high concentration of streptomycin was determined by comparing the number of colonies growing from equal inocula in 2 pour plate preparations of Bordet-Gengou agar, 1 with streptomycin and 1 without this antibiotic. The inoculum was a suspension in broth of a 24 hr. old growth on Bordet-Gengou agar, adjusted to yield a turbidity of 150 on the Klett-Summerson photoelectric colorimeter filter 54 (2 billion viable organisms/cc.) and diluted to 10^{-7}; 0.5 cc. was used as the test inoculum for each of the 2 pour plates.

A number of bacterial species when large populations are seeded in pour plate preparations of agar containing high concentrations of streptomycin form 2 kinds of colonies containing highly resistant cells; in 1 the organisms grow equally well in the presence and absence of streptomycin and in the other they grow poorly or not at all in the absence of high concentrations of streptomycin. Resistant colonies of H. pertussis and H. parapertussis which formed in pour plate preparations of Bordet-Gengou agar containing streptomycin were studied from this viewpoint. Each colony

tested was suspended in 0.1 cc. of broth and a 2 mm. loopful seeded on Bordet-Gengou agar with and without streptomycin.

Examination for Trait 3: Rate of Occurrence of H. Pertussis and H. Parapertussis Cells Resistant to a High Concentration of Streptomycin:—The procedure used for this purpose was similar to that described for examination of Trait 1, with 1 modification: a small initial seeding population was required to ensure that the resistant colonies growing in the pour plates containing streptomycin represent new mutants and not those resulting from reproduction of resistant cells in the broth culture used for seeding. For this purpose it was necessary to start with a broth suspension which contained a small enough number of organisms to make the presence of a highly resistant variant unlikely. Suitable suspensions were prepared in the following way for both H. pertussis and H. parapertussis. Growth on a Bordet-Gengou agar plate after 24 hrs.' incubation was suspended in 12 cc. of broth; H. pertussis suspension, diluted 50-fold, was seeded in 1 cc. quantities on the surface of 10 Bordet-Gengou agar plates; H. parapertussis was diluted 100-fold and 0.5 cc. inoculated on 10 Bordet-Gengou agar plates. After incubation for 30 hrs. the growth of each was removed by washing with 3.5 cc. of broth and transferred to a separate tube. From this point the procedure is identical with that used for study of Trait 1. In order to determine the size of the initial population seeded for production of multiple independent cultures an appropriate dilution was inoculated into a Bordet-Gengou pour plate preparation; to examine this inoculum for presence of highly resistant variants 2 cc. was seeded into each of 5 pour plates of Bordet-Gengou agar containing the appropriate concentration of streptomycin. A graph and an equation reported by Luria and Delbrück[33] were used for determining the rate of occurrence of new resistant variants by supplying the values for the average number of resistant colonies growing on each of 10 plates seeded from 10 independent cultures, the population seeded into each plate, and the number of plates used.

TABLE I

IRREGULAR DISTRIBUTION OF RESISTANT VARIANTS IN EQUAL INDEPENDENT POPULATIONS OF SAME STRAIN AS COMPARED WITH SAMPLES OF POOL

Species / Strain No.	Prevalence Resistant Cells in Inoculum	Source of Cultures	Total Bacteria Examined	Resistant Colonies	
				Total	Number per Plate
H. pertussis No. 1	$1:3.5\times10^9$	Pool	Billions 124	42	6-1-5-1-1-2-11-3-9-3
		Indep't	248	122	0-2-0-55-1-0-0-0-0-0-0-2-0-62-0-0-0-0-0-0
H. pertussis No. 2	$1:5\times10^9$	Pool	146	133	11-15-10-15-14-9-20-17-10-12
		Indep't	292	253	0-0-0-0-1-2-0-0-5-0-0-0-0-0-0-0-238-0-0-7
H. parapertussis No. 1	$1:0.8\times10^9$	Pool	56	93	6-9-9-12-9-8-7-9-10-14
		Indep't	56	85	1-4-23-3-2-2-3-41-3-3
H. parapertussis No. 2	$1:0.04\times10^9$	Pool	190	3,517	351-331-364-336-358-374-347-358-344-354
		Indep't	190	3,253	372-305-247-258-323-420-247-570-360-151

Indep't = Independent.

Experimental Results

To demonstrate that the highly resistant cells of H. pertussis and H. parapertussis occur spontaneously and are present initially in all large populations, experiments were performed to show that populations of the same size when they are derived from independent cultures of the same strain show widely varying numbers of highly resistant colonies when seeded into agar pour plate preparations containing high concentrations of streptomycin. The results are listed in Table I. The similar population sizes grown from the same strain but derived from a single source form approximately the same numbers of resistant colonies in each pour plate of agar containing streptomycin. It is apparent from the results of 2 experiments on each of these organisms that the irregular distribution of resistant variants precludes any action of the streptomycin in their development and presents evidence for their presence in the suspensions before exposure to the antibiotic.

TABLE II

Inheritance of Resistance Trait by Descendants of Variant Cells Forming Colonies During First Exposure to Streptomycin

Species	Strain Number	Colonies Growing from Equal Inocula in Presence and Absence of Streptomycin After 1, 10 and 20 Subcultures Free of Streptomycin					
		1		10		20	
		0*	SM†	0	SM	0	SM
H. pertussis	1	46	112	194	194	240	246
	3	282	274	312	248	252	208
H. parapertussis	2	148	114	200	200	160	176
	1	119	132	192	162	164	192

* No streptomycin.

† 100 mcg. of streptomycin per cc. used for H. pertussis.
1,000 mcg of streptomycin per cc. used for H. parapertussis.

TABLE III

Data from Experiments Which Studied Rate of Occurrence of Mutants Resistant to High Concentrations of Streptomycin

Species	Strain Number	Broth Inoculum Used for Seeding Independent Cultures			Resistant Colonies in Independent Cultures			
		Prevalence Resistant Colonies before Dilution	Dilution Seeded	Total Organisms Seeded	No. of Cultures	Average No. Resistant Colonies per Culture	Organisms per Culture Billions	Mutation Rate per Bacterium per Bacterial Generation
H. pertussis	3	$1:36.0\times10^{9}$	none	18.0×10^{9}	10	1.6	15.4	5.2×10^{-11}
	4	$1:3.6\times10^{9}$	1:100	4.4×10^{8}	10	1.2	6.2	1.1×10^{-10}
	5	$1:12.0\times10^{9}$	1:50	4.8×10^{8}	10	5.0	11.0	1.6×10^{-10}
H. parapertussis	3	$1:0.2\times10^{9}$	1:100	7.5×10^{7}	10	2.0	14.4	6.6×10^{-11}
	4	$1:0.3\times10^{9}$	1:100	1.7×10^{8}	10	15.5	19.0	6.1×10^{-10}
	5	$1:1.2\times10^{9}$	1:100	2.6×10^{8}	10	5.5	15.3	1.2×10^{-10}

Data presenting evidence for inheritance of the resistance trait are shown in Table II. Two resistant colonies of each species, H. pertussis and H. parapertussis, were subcultured 20 times at 24 to 48 hr. intervals in the absence of streptomycin. After 1, 10 and 20 subcultures the degree of resistance of their progeny was tested by comparing the number of colonies which grew from equal inocula in 2 pour plate preparations, 1 containing streptomycin and 1 without the antibiotic. The results show that after each of these periods of growth in the absence of streptomycin the entire population continued to be resistant to high concentrations of streptomycin. Therefore, the resistant trait can be assumed to be inherited.

Table III lists the data from experiments on 3 strains of H. pertussis and H. parapertussis to determine the frequency of occurrence of new resistant variants. The method of Luria and Delbrück[13] was used for these calculations. The details of application in studying H. influenzae have been reported.[8] The rate of occurrence of highly resistant cells in all strains of both species is very low and consistent with mutation frequency; this trait appears to be constant for all strains of a species.

TABLE IV

GROWTH CHARACTERISTICS OF COLONIES WHICH FORM IN MEDIA CONTAINING HIGH CONCENTRATIONS OF STREPTOMYCIN

Species	Total Resistant Colonies Studied	Number of Colonies Showing Following Traits	
		Comparable Growth in Presence and Absence of Streptomycin*	Grow Well on Streptomycin* Agar; Poor or No Growth Without Streptomycin
H. pertussis	237	230	7
H. parapertussis	180	174	6

* 100 mcg./cc. used for H. pertussis.
1,000 mcg./cc. used for H. parapertussis.

It is seen that populations of H. pertussis and H. parapertussis do not differ in the frequency of new highly resistant mutants.

From each experiment performed to determine the mutation rate on each of these organisms, a number of the colonies were selected for study of their growth capacities in the presence and absence of streptomycin to determine whether some of the highly resistant members had so changed in their growth requirements that they depended upon the antibiotic for growth. Table IV lists the results. Out of 237 H. pertussis highly resistant mutants, 7 exhibited evidence of streptomycin dependence; of 180 H. parapertussis resistant colonies, 6 grew poorly or not at all in the absence of streptomycin.

DISCUSSION

The results of this investigation furnish two more examples of application of the principle that emergence of resistance to streptomycin during treatment is the result of the selective action of the antibiotic which by eliminating the sensitive members allows the small number of resistant mutants, through their reproduction, to make up most or all of the population.

The authors' limited experience with the streptomycin treatment of pertussis caused by H. pertussis suggests that the course of the disease is significantly altered. In a series of 15 young infants treated with streptomycin by the intramuscular route only, 40 mg./kg./day for 4 to 6 days, emergence of resistance of H. pertussis to streptomycin was not demonstrable in any case, even though organisms persisted in the nesopharynx for some time after streptomycin therapy; in all cases the organisms showed the usual

degree of sensitivity to streptomycin. It is believed that in this location streptomycin is not sufficiently in contact with the organisms to exert its selective action by killing off the sensitive members. On the other hand, emergence of resistance to streptomycin has been reported by Bradford[14, 15] when the antibiotic is used as an aerosol in treating pertussis.

Experience with this antibiotic in H. parapertussis infections is not yet available but *in vitro* studies suggest that it will be unsuccessful therapeutically. Recent investigations to be published[16] indicate that knowledge of two factors *in vitro* may serve as a reliable basis for predicting the success or failure of streptomycin therapy in infections caused by gram negative bacilli. The results show that in species which produce infections in which streptomycin has been a valuable therapeutic agent, the antibiotic is rapidly bactericidal on the sensitive cells in concentrations readily and safely attained in blood. Moreover, while the mutation rate of highly resistant variants gives no clue, the frequency of occurrence of mutants resisting lower concentrations of streptomycin, 25 and 100 mcg./cc., appears to be closely related to therapeutic efficacy of streptomycin among infections caused by gram negative bacilli. The frequency of the less resistant mutants is just as low as that of the highly resistant mutants in species which cause infections successfully treated with streptomycin; but in species responsible for infections in which streptomycin has not been effective—for example, typhoid fever, Salmonella and Ps. aeruginosa infections—the rate of occurrence of new mutants resisting 25 and 100 mcg./cc. is 10,000 to 100,000 times more frequent than of those capable of growth in 1000 mcg./cc. Analysis of these two factors in H. pertussis and H. parapertussis populations leads one to predict therapeutic success of streptomycin in H. pertussis infections and failure in those caused by H. parapertussis. While their mutation rates with respect to the highly resistant variants do not differ, the frequency of occurrence of mutants resisting 25 mcg. and 100 mcg. of streptomycin/cc. is much higher in H. parapertussis populations. Moreover, concentrations of streptomycin easily and safely obtainable in body fluids kill 100% of sensitive H. pertussis cells in 4 to 24 hours, whereas, approximately 100% of H. parapertussis cells persist after 6 hours, and even after 24 hours a small fraction is viable. The routine *in vitro* sensitivity tests suggest a great difference in susceptibility of the two species. The minimal effective concentration required for H. pertussis has varied from 3 to 10 mcg./cc., and for H. parapertussis from 100 to 200 when tested by the procedure described for H. influenzae.[17]

Summary

In large populations of H. pertussis and H. parapertussis which have never been exposed to streptomycin, it is possible to demonstrate the presence of cells resistant to streptomycin 1000 mcg./cc.

These highly resistant cells exhibit the following traits which are characteristic of mutants: 1. Irregular occurrence in different independent cultures of same population size and strain and therefore independence of the action of streptomycin. 2. Transmission of the resistant trait unchanged in degree through many subcultures in the absence of streptomycin and, therefore, inheritance of the trait. 3. A rate of occurrence consistent with mutation frequency; the mutation rate of cells resistant to 1000 mcg./cc. does not differ significantly between these two species.

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Spanish Abstract

Mecanismo de Emergencia de Resistencia de Estreptomicina de H. Pertussis y H. Parapertussis Durante el Tratamiento con Este Antibiótico

En poblaciones grandes de H. Pertussis y H. parapertussis que nunca han sido expuestas a la estreptomicina, es posible demostrar la presencia de células resistentes a la estreptomicina 100 mcg./cc.

Estas células altamente resistentes muestran los siguientes rasgos que son característicos de mutantes: 1. Aparecimiento irregular en diferentes cultivos independientes del mismo tamaño de la población y cepa y por consiguiente independencia de la acción de la estreptomicina. 2. Transmisión del rasgo resistente inalterable en grado a traves de los muchos sub-cultivos en la ausencia de la estreptomicina y, por consiguiente, la herencia del rasgo. 3. Una proporción de casos consistentes con la frecuencia de mutación; la proporción de mutación de células resistentes a 1000 mcg./cc. no difiere grandemente entre estas dos especies.

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IMMUNIZATION AGAINST PERTUSSIS DURING THE FIRST FOUR MONTHS OF LIFE

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SUCCESSFUL immunization of infants against pertussis when injections of vaccine were begun as early as the second month of age was reported in 1945 by Sako, Treuting, Witt and Nichamin.[1] In a group of 3793 infants, 1834 of which had received a total dose of 40 billion H. pertussis, alum-precipitated, they observed 308 familial exposures during a period of 27 months. The secondary familial attack rate in 159 exposed vaccinated infants was 18.9% and in 149 unvaccinated infants was 85.2%. The difference in attack rates was 66.3% ± 5.7% which is, of course, statistically significant. This report reopened the possibility of protecting against pertussis at the age when the disease is most dangerous.

No field study similar to Sako's on the clinical effectiveness of H. pertussis immunization at the age of one to four months has been published, as far as is known. Direct confirmation of these observations is thus not available. However, several other studies have contributed indirect evidence by means of serologic or dermal estimations of the immune response. They will be discussed later.

Indirect evidence may have to be utilized in communities (such as San Francisco) where the incidence of pertussis has become too low, as a result of general immunization, for satisfactory field trials. Serologic evidence provided by a technic which has previously been correlated with the clinical test of household exposure is obviously of more value than serologic estimations with technics which have not been so compared. Apparently only two such "tests of immunity" have thus been actually tried in the field—the agglutinogen skin test of Felton and Flosdorf[2] and the agglutinative reaction devised in this laboratory.[3] With the latter technic, it was observed during a four year study[4] that vaccinated children carrying agglutinins in serum dilutions of 1-320 or higher did not contract pertussis after household exposure. Children with lower titers or with no agglutinins, however, were not necessarily susceptible. Sako,[5] employing the same technic, was able to confirm and extend this relationship. In vaccinated children with titers below 1-320, he observed that the secondary familial attack rate varied inversely with the titer and that it reached a maximum of 33% when no agglutinins were present.

Serum agglutinins (as determined by the above technic) are absent or present in very low titer in children who have not received vaccine.[3] During an attack of pertussis, agglutinin production is less constant than after inoculation with vaccine and these antibodies often disappear within a few months after recovery.[3] Thus it is believed that, while clinical immunity is by no means dependent on circulating antibodies, their demonstration in high titer over a period of time following vaccine can be employed as an index of the effectiveness of an immunizing agent.

The following studies with this serologic technic were undertaken to obtain additional

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evidence for or against the use of H. pertussis vaccine under the age of six months. Since the program involved an attempt at active immunization beginning in the neonatal period, it was necessary first to determine to what degree H. pertussis agglutinins had passed transplacentally from mother to child.

Observations

Comparison of Maternal and Cord Bloods

Agglutinative reactions were performed on 108 pairs of maternal and umbilical cord sera. None of the mothers had had H. pertussis vaccine or pertussis during pregnancy. The results are shown in Table I. Note that none of the mothers carried high titers of 1-320 or more. There was an exact correspondence of agglutinative titer in 61 pairs (56%), and correspondence within 1 dilution (limits of experimental error) in 22 pairs. The correspondence within the range of error was therefore 77%.

TABLE I

Correlation between Maternal and Umbilical Cord Serum Agglutinins—108 Pairs

Maternal Serum		Negative	Cord Serum: Positive in Dilution of						Total (Maternal)	Per Cent
			1–10	1–20	1–40	1–80	1–160	1–320		
Positive in dilution of	1–320									
	1–160		1			1	2	1	5	4.6%
	1– 80	5	1	1	1	2			10	9.3%
	1– 40	5	3	7	3				18	16.7%
	1– 20	6	3	3	1				13	12.0%
	1– 10	4	2	1	1				8	7.4%
Negative		49	3	1	1				54	50.0%
Total (Cord)		69	13	13	7	3	2	1		
Per Cent		63.8%	12.0%	12.0%	6.5%	2.8%	1.9%	0.9%		

Exactly half, 54, of the maternal sera contained agglutinins. Thirty-four of the offspring of these 54 women had agglutinins in their cord sera. Thus transplacental transmission of antibody was demonstrated in 63% of sero-positive mothers. Agglutinins in very low titer were also demonstrated in the cord sera of 5 infants of sero-negative mothers. This finding can be explained only on the possible basis of hemoconcentration in the infants or hemodilution in the mother.

When placental transmission occurred, the relationship between the maternal and cord blood agglutinin titers was as follows: In 6 instances the cord titer was significantly (more than 1 tube dilution) lower. In 30 instances, the cord and maternal titers corresponded within 1 dilution. In 3 instances, the cord titer was significantly higher.

It appears then that in this community about one half of the women of childbearing age carry serum antibody against pertussis and about one third of the newborn infants exhibit placentally transferred antibody. If the presence of passively acquired antibody interferes with active immunization, one might possibly expect difficulty (in this community) in immunizing at least one third of the infants (until such time as the antibody has disappeared).

Administration of Saline-Suspended H. Pertussis Vaccine to Newborn Infants

Active immunization with saline-suspended H. pertussis vaccine* was attempted in the following manner: The 1st injection was given 5 days after birth, a 2nd injection at 1 mo. of age, and a

* Supplied by the Cutter Laboratories, Berkeley, Calif.

TABLE II

AGGLUTINATIVE TITERS IN 41 INFANTS IN GROUP 1 WHO RECEIVED TOTAL OF 50 BILLION SALINE SUSPENDED H. PERTUSSIS

Titer	Before 1st Injection	At 2nd Injection	At 3rd Injection	1 Mo. After 3rd Injection	At 4th Injection (booster)
	Age				
	Newborn (cord)	1 Mo.	2 Mos.	3 Mos.	6 Mos.
1–1,280					1
1– 640				3	2
1– 320	1			1	
1– 160	1	1		5	1
1– 80		1	5	4	
1– 40	4		2	5	1
1– 20	5		4	2	1
1– 10	2	2	5		
Neg.	28	35	17	6	
Total	41	39	33	26	6
Per cent with 1–320 or more	2%	0%	0%	15.4%	

TABLE III

AGGLUTINATIVE TITERS IN 145 INFANTS IN GROUP 2 WHO RECEIVED TOTAL OF 100 BILLION SALINE SUSPENDED H. PERTUSSIS

Titer	Before 1st Injection	At 2nd Injection	At 3rd Injection	1 Mo. After 3rd Injection	At 4th Injection (booster)
	Age				
	Newborn (cord)	1 Mo.	2 Mos.	3 Mos.	6 Mos.
1–1,280				6	1
1– 640	1		1	15	
1– 320	3		4	8	1
1– 160	1		8	10	1
1– 80	10		7	15	1
1– 40	9		8	19	
1– 20	10	2	14	5	3
1– 10	11	1	13	3	
Neg.	78	7	49	34	3
Total	123	10	104	115	10
Per cent with 1–320 or more	3.3%		4.8%	25.2%	

Cord blood was not tested in 22 instances.

3rd injection at 2 mos. of age. Obviously, some leeway as to these days occurred. At 6 mos. of age, an injection of combined diphtheria and tetanus toxoids (aluminum hydroxide-adsorbed) containing H. pertussis vaccine, 20 billion/cc., was given.

In the 1st group—41 babies—a total dose of 50 billion cells divided into doses of 10, 20 and 20 billion was given. The results of the agglutinative reactions are shown in Table II. As no relation between the presence or absence of agglutinins in the cord blood and the immune response was apparent, all the titrations appear in this table. The titers observed in these infants are, with few exceptions, very low. Only 4 (15.4%), of 26 sera tested 1 mo. after the 3rd injection, at 3 mos. of age, showed agglutinins in a titer of 1-320 or higher. Furthermore, 3 babies with negative cord blood failed to produce any agglutinin and 3 more with positive cord blood lost their antibody. It was apparent that with the dose of vaccine used antibody production was poor.

In the 2nd group, a total dose of 100 billion saline-suspended H. pertussis was divided into doses of 20, 40 and 40 billion cells. The intervals were the same as previously used. 145 newborn infants were injected. The results of the agglutinative reactions are shown in Table III.

TABLE IV

232 Agglutinative Tests on 134 Children in Group 3 Who Received Total of 80 Billion Saline Suspended H. Pertussis

Titer	Weeks after 3rd Injection				
	4–8 Wks.	12–14 Wks.	15–23 Wks.	24–28 Wks.	29–51 Wks.
1–1,280	16	5	1		2
1– 640	17	8	4	9	3
1– 320	18	7	7	1	2
1– 160	14	3	7	6	1
1– 80	9	6	6	3	3
1– 40	13	5	1	1	1
1– 20	7	8	2	3	
1– 10	1				
Neg.	10	13	2	4	3
Total	105	55	30	27	15
Per cent with 1–320 or more	48.5%	36.3%	40.0%	37.0%	

There is only 1 test per child in each time interval.

Twenty-nine (25.2%) of 115 sera examined 1 mo. after the 3rd injection contained agglutinins in dilutions of 1-320 or higher. These high titers appeared in almost identical percentages in cord blood positive and cord blood negative infants. Thirty-four (29.8%) of the infants tested 1 mo. after the 3rd injection had entirely negative sera. Sixteen of these had had negative cord blood, 8 had lost their passively acquired antibody and the remainder had not been tested at birth.

Thus with a total dose of 100 billion saline-suspended cells a slightly higher percentage of infants exhibited high titers than when 50 billion cells were used. The difference, however, between 25.2% and 15.4% (9.8% $\pm$ 9.1%) is not statistically significant. With these doses of saline-suspended vaccine commenced at 5 days of age, the percentage of infants developing a good serologic response is certainly unsatisfactory. The presence or absence of transplacentally acquired agglutinins did not appear to influence the capacity of the infant to manufacture his own antibody.

One child in the 2nd group is believed to have had pertussis at the age of 2½ yrs. Details of exposure are not known.

No general reactions to the vaccine other than slight fever occurred in these 2 groups. Local reactions were not marked.

Administration of Saline-Suspended H. Pertussis Vaccine Beginning at Four to Eight Weeks of Age (Group 3)

Saline-suspended vaccine (40 billion cells/cc.) was administered to 134 infants beginning at 4 to 8 wks. of age. The 1st injection consisted of 0.4 cc. (16 billion cells). Four wks. later, 0.6 cc. (24 billion cells) was given and 4 wks. after that, 1.0 cc. (40 billion cells). These time intervals corresponded to those employed by Sako in his successful venture with alum-precipitated vaccine at this age. The total dosage of 80 billion was twice that employed by Sako with alum-precipitated vaccine.

Eleven instances of moderate or marked febrile reactions occurred. In none were there convulsions. Three reactions followed the 1st injection, 4 the 2nd injection and 3 the 3rd injection. Following the reactions, injections were always made with smaller doses. Repeated reactions in the same child were thereby prevented. No marked local reactions occurred.

TABLE V

343 Agglutinative Tests on 151 Children in Group 4 Who Received Total of 40 Billion Alum-Precipitated H. Pertussis

Titer	Weeks After 3rd Injection					
	4–8 Wks.	12–14 Wks.	15–23 Wks.	24–28 Wks.	29–51 Wks.	52 Wks. or More
1–1,280	24	11	9	7	7	11
1– 640	24	15	7	10	13	13
1– 320	24	11	7	6	8	6
1– 160	15	8	4	9	9	8
1– 80	14	7	5	4	6	7
1– 40	6	4		2	2	2
1– 20	1		1			2
1– 10						
Neg.	7	3	2		1	1
Total	115	59	35	38	46	50
Per cent with 1–320 or more	62.6%	62.7%	65.7%	60.5%	60.9%	60.0%

There is only 1 test per child in each time interval.

Agglutinative tests were performed subsequently and are recorded in Table IV. 48.5% of infants attained agglutinative titers of 1-320 or higher when tested 4 to 8 wks. after completion of the course. Ten of 105 infants (9.5%) failed to produce agglutinins. During the following 6 mos., the per cent of infants who maintained titers of 1-320 or higher decreased to between 36 and 40%.

Although these serologic responses to 80 billion saline-suspended H. pertussis in the age group under question are superior to those reported by Sako[5] with 100 billion saline-suspended cells, they are inferior to the results previously reported[6] with this dose at 6 mos. of age. In our older age group, over 60% of infants maintained high titers for 4 yrs. Thus, age appears to be a factor in the serologic response to immunization with 80 billion saline-suspended H. pertussis. When injections are begun at 4 to 8 wks. of age instead of 6 mos. of age, fewer infants manufacture agglutinins in high titer and titers are not so well maintained.

One infant in this group contracted pertussis from his mother 6 mos. after completion of his injections.

Administration of Alum-Precipitated H. Pertussis Vaccine Beginning at Four to Eight Weeks of Age (Group 4)

The procedures employed by Sako, Treuting, Witt and Nichamin[1] were duplicated. Alum-

precipitated vaccine,* 40 billion cells/cc., was given intramuscularly in divided doses of 0.2 cc., 0.3 cc. and 0.5 cc., at monthly intervals. The 1st injection was made at 4 to 8 wks. of age. (The total dose of 40 billion cells was thus less than in the previous groups where saline-suspended vaccine was employed.)

Fortunately, there were few reactions to these injections. One infant reacted with a high fever (temperature, 40°C.), vomiting and diarrhea to his 3rd injection. He also had a marked local reaction which did not break down. There were no neurologic sequelae. Another infant had a marked febrile reaction following his 2nd injection of vaccine. The 3rd dose was therefore divided into 2 injections. These produced no reactions.

It is believed this good fortune is related to injecting the alum-precipitated vaccine intramuscularly and to prescribing 1 grain of acetylsalicylic acid 4 hrs. and again 8 hrs. after the injection.

Agglutinative reactions were performed 4 to 8 wks. after the 3rd injection (that is, in the 5th mo. of life) and repeated at later intervals. The serologic responses observed in 151 infants appear in Table V.

It is apparent that the serologic titers attained in this group of infants were higher than in those previously discussed. At 4 to 8 wks. after completion of the course, 62.6% of the infants tested exhibited titers of 1-320 or higher as compared to 48.5% of the infants of similar age in Group 3. The difference ($14.1\% \pm 6.6\%$) is 2.1 times the standard error. Much more significant is the observation that following alum-precipitated vaccine 60% of the infants maintained high titers for 1 yr. A statistically significant difference in the per cent of infants with titers of 1-320 or higher is observed at 12 to 14 wks. after vaccination. ($26.4\% \pm 9.3\%$ or $2.8 \times$ standard error.)

These fortunate results with alum-precipitated vaccine confirm those reported by Sako[6] with the same vaccine, dosage, age group and agglutinative technic. He reported that 50.5% of infants exhibited titers of 1-320 or more 2 to 4 mos. after this course of vaccine. Furthermore, he noted that little change in titer occurred for at least 3 yrs. following alum-precipitated vaccine. This persistence of serum agglutinin on a "plateau" has also been noted previously in this laboratory[6] following the immunization of older infants and children (6 to 36 mos. of age) with 80 billion saline-suspended H. pertussis.

There have been no known cases of pertussis in these infants who received alum-precipitated vaccine. Likewise, there have been no known exposures, though it must be admitted that close follow-up has been impossible.

Discussion

The transplacental transmission of H. pertussis serum antibody has been demonstrated by various means in the past. Weichsel and Douglas,[7] employing the complement fixation reaction for H. pertussis on 20 pairs of maternal and cord blood sera, demonstrated transplacental transmission in three instances. Bradford, Slavin and Lichty[8, 9] showed that a high opsonocytophagic index in the newborn was associated with a higher index in the mother. This was confirmed by Rambar and his associates[10] who found that opsonins may persist in infants' sera for nine weeks after birth. Kendrick, Thompson and Eldering[11] studied the opsonocytophagic index of women immunized with H. pertussis vaccine during pregnancy. They noted that the higher the index of the mother's blood, the more nearly did the index of her infant approach her own. Cohen and Scadron[12] administered H. pertussis vaccine to women in the third trimester of pregnancy and demonstrated mouse protective antibodies in high titer in all of 27 pairs of maternal and cord sera. In the infants of uninoculated mothers, mouse protective antibodies usually could not be demonstrated.

Adams, Kimball and Adams[13] tested 142 pairs of maternal and cord blood sera for H. pertussis agglutinins. No agglutinins were found in 77% of the pairs. Transplacental transmission of agglutinin was demonstrated in 18 of 33 sero-positive mothers,

* Supplied by Eli Lilly and Co., Indianapolis, Ind.

54.5% as compared to the finding in this study of 63%. In another group of 16 women, H. pertussis vaccine (100 billion cells) was administered in the third trimester of pregnancy. Whereas all of the injected women showed a serologic response, their titers at term varied 64 fold (from 1-40 to 1-2560). Four of the 16 cord blood specimens contained no agglutinins and the majority exhibited titers lower than that of the corresponding maternal blood. "During the first 6 months of life the titer was gradually lost."

It would seem that the following conclusions may be drawn from these observations: In different communities the percentage of women of childbearing age carrying H. pertussis serum antibodies varies. Usually it is less than 50%. Transplacental transmission of antibody in low titer may be expected in about 60% of such sero-positive women. Therefore probably not more than 25% of infants are born with circulating antibodies. These disappear within a few months. If, as the authors believe, immunity to pertussis is dependent upon the destruction of the invading organism in or on the mucosa of the respiratory tract, it seems most unlikely that transplacentally acquired antibodies could ever achieve sufficient concentration to saturate this line of defense. Clinical experience certainly bears this out. Furthermore, in view of the findings just reported, it seems unlikely that transplacentally acquired antibody is ever present in sufficient concentration to block active immunization with vaccine.

When pregnant women in the third trimester are injected with H. pertussis vaccine, their serum will contain antibody in widely varying concentration. The great majority of their infants will be born with passively acquired antibody often in high titer. However, there exists no proof as far as is known that these infants are clinically immune. It would seem that the inoculation of women during pregnancy is too uncertain a procedure to be recommended.

The evidence that effective immunization against pertussis may be accomplished before six months of age with alum-precipitated vaccine in a total dose of 40 billion cells may be summarized as follows: Sako and his coworkers[1] demonstrated statistically significant protection against familial exposure with this product and this dosage. At the same time,[5] he demonstrated that immunity was associated with the carriage of serum agglutinins in titers of 1-320 or more. Using the same product and the same agglutinative technic, in this study the production of agglutinins in high titer in a similar (slightly higher) per cent of infants has been observed. Using the same alum-precipitated vaccine, Halpern and Halpern[14] demonstrated agglutinin production by another technic and also demonstrated strongly positive (immune) skin reactions with agglutinogen.

With a different product (aluminum hydroxide-adsorbed diphtheria and tetanus toxoids containing H. pertussis vaccine), Peterson[15] and di Sant'Agnese[16, 17] likewise observed H. pertussis agglutinin production at a similar age. Di Sant'Agnese began inoculations at one week of age and reinjected this triple antigen at five and at nine weeks of age. The total dose of H. pertussis was 50 billion cells. The initial serologic response in his group of infants to the H. pertussis component in the antigen was similar to that obtained in this laboratory and by Sako with alum-precipitated vaccine. Fifty-four per cent of infants developed agglutinins in a titer of 1-400 or more. However, four months later this proportion had dropped to 33%. Reinjection then, or later, resulted in high titers in slightly over 60% of the infants. The declining titer of agglutinins found by di Sant'Agnese in a considerable proportion of his patients is similar to that observed in this study after saline-suspended vaccine (Group 3). His reported loss of

titer would seem to be the result of commencing inoculations at one week of age. In older infants it has previously been found[18] that aluminum hydroxide adsorbed triple antigen induces high titers in the majority of infants with little or no decline in two years. It would seem, therefore, that commencing active immunization with adsorbed or precipitated vaccine at one week of age will achieve less protection than commencing at four to eight weeks of age.

What percentage of infants maintaining agglutinin titers of 1-320 or more should be considered satisfactory? Can the indirect evidence obtained from the serum titrations be used to approximate the percentage of infants likely to be actually protected? In order to attempt to answer this, the data reported from this clinic several years ago[4] (see also Addendum) may be summarized as follows: The carriage of agglutinins in a titer of 1-320 or more by 61% of children subjected to household exposure was associated with a secondary attack rate of 9%. The secondary attack rate for noninoculated children up to four years of age was found by Wheeler[19] to be 92.8%. (Sako's figure[5] is 89.7%.) Subtracting the secondary attack rate in immunized infants (9%) from that given for noninoculated infants (90%) yields 81% presumably protected by the vaccine. The ratio, per cent protected / per cent with titers of 1-320 or more, is thus .81/.61 = 1.33. In other words, the percentage of children protected was 1.33 times the percentage carrying titers of 1-320 or higher. This estimate probably errs on the safe side.

If this formula is employed, it is apparent that when agglutinin titers of 1-320 or more are attained and maintained by 70% of the individuals in an inoculated group, then 93% might be protected. This result should be considered highly satisfactory. On the other hand, if less than 50% of children maintained high titers, then less than 66% of children might be protected against familial exposure. This should not be considered satisfactory.

The evidence that saline-suspended vaccine is not as effective as precipitated vaccine in infants under the age of six months may be summarized as follows: Direct comparison of the serologic response following the administration of these agents was made by Sako[5] and in this laboratory. Following saline-suspended vaccine, fewer infants developed high titers and a decline in titer within a few months frequently occurred. The reports of other workers,[13, 20, 21] who employed only saline-suspended vaccine show a wide variability in serologic response.

In conclusion, it is submitted that there is sufficient evidence to recommend the administration of alum-precipitated H. pertussis vaccine in early infancy. The following immunization schedule is therefore suggested:

I. 4 to 6 weeks of age II. 8 to 10 weeks of age III. 12 to 14 weeks of age	Three injections of alum-precipitated H. pertussis vaccine intramuscularly. The total number of cells should be at least 40 billion and the volume of any one injection should not exceed 0.5 cc.
IV. 6 months of age	Combined alum-precipitated (or aluminum hydroxide-adsorbed) diphtheria and tetanus toxoids in a volume of 0.5 cc.
V. 9 months of age	Repeat IV.
VI. 12 months of age	Smallpox vaccination.
VII. 15 months of age	Combined alum-precipitated (or aluminum hydroxide-adsorbed) diphtheria and tetanus toxoids containing H. pertussis vaccine. Ten billion cells are adequate and the volume should not exceed 0.5 cc.

The last injection should be considered an integral part of the course of tetanus immunization and a secondary stimulus ("booster") to pertussis immunity. It has been shown[22] that three injections of precipitated tetanus toxoid result in more prolonged maintenance of high antitoxin titers than do two injections. The wide time intervals (three and six months, respectively) suggested between the three injections of toxoids likewise make for higher and more durable tetanus antitoxic immunity than do conventional one month intervals.[23, 24] The age of 15 months is selected for this injection of triple combined antigens because it is approximately 12 months after completion of the early course of H. pertussis vaccine. A secondary stimulus to pertussis immunity is advisable at this time. The presence of diphtheria toxoid in this 15th month inoculation is not essential. However, as tetanus toxoid-H. pertussis vaccine (double) mixtures are not available commercially, the triple antigen mixture is conveniently employed here. Its effectiveness in the combined primary immunization of infants six months of age or older has been amply demonstrated.[18, 25-27] On the other hand, its use during the first three months of life, as recently described by di Sant'Agnese,[16, 17] involves two questions: (a) that of the necessity of giving diphtheria and tetanus toxoid at this age; (b) that of the effectiveness of the immune response to diphtheria toxoid in the presence of transplacentally acquired diphtheria antitoxin. It is not within the scope of this report to discuss the limited and conflicting evidence[15, 17, 28] now available on the latter question.

Summary

Agglutinative reactions with H. pertussis were performed on 108 pairs of maternal and cord blood sera. A correspondence in titer within the range of experimental error was demonstrated in 77% of the pairs. Fifty per cent of the maternal sera contained demonstrable agglutinins. Transplacental transmission of antibody was demonstrated in 63% of the 54 sero-positive mothers.

Saline-suspended H. pertussis vaccine was administered to infants on the fifth day of life and repeated at one and at two months of age. With total doses of 50 billion H. pertussis only 15% of 41 infants produced agglutinins in a titer of 1-320 or higher—the level which in older children has been found consonant with clinical immunity. When the total dose in a second group of infants was increased to 100 billion H. pertussis, the above titer was demonstrated in 25% of 145 infants.

The serologic response of infants whose cord blood had contained no agglutinins was not superior to that of infants with agglutinins. Thus no depression of the immune response by transplacentally acquired antibody was demonstrable.

In a third group of 134 slightly older infants, saline-suspended H. pertussis vaccine was administered in a total dose of 80 billion cells divided into three monthly injections. The first injection was given at four to eight weeks of age. Forty-eight per cent of these infants manufactured agglutinins in a titer of 1-320 or higher. However, three months later only 36% were carrying this high titer. General febrile reactions were not uncommon and one proved case of mild pertussis occurred in this group.

In a fourth group of 151 infants, alum-precipitated H. pertussis vaccine was injected in a total dose of 40 billion cells divided into three injections at monthly intervals. The first injection was given at four to eight weeks of age. Only two febrile reactions, one associated with a local reaction which did not break down, occurred. Sixty-two per cent of 115 infants whose sera were tested four to eight weeks later developed H. pertussis agglutinins in a titer of 1-320 or higher. Twelve months later 60 per cent still carried

these high titers. This satisfactory response at this age with this product is confirmatory of the studies of Sako, Treuting, Witt and Nichamin. It adds support to their thesis that active immunization with alum-precipitated vaccine can be accomplished before the sixth month of life.

A schedule for immunizations during the first year of life, embodying H. pertussis immunization beginning at four to eight weeks of age, is described.

Conclusion

Active immunization against pertussis is practicable and effective beginning at four to eight weeks of age when alum-precipitated vaccine is used. Saline-suspended H. pertussis vaccine is not as effective at this age.

Addendum

Additional evidence in support of the above conclusion is given in Bell, J. A., Pertussis immunization: Use of two doses of an alum-precipitated mixture of diphtheria toxoid and pertussis, J.A.M.A. **137**:1276, 1948.

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SPANISH ABSTRACT

Inmunización Contra Pertussis Durante los Primeros Cuatro Meses de Vida

Se hicieron reacciones aglutinantes con H. pertussis en 108 pares de sueros de sangre de la cuerda y materno. Una correspondencia en título dentro del círculo de error experimental fué demostrado en 77% de los pares. Cincuenta por ciento de los sueros maternos contenían aglutininas demostrables. Transmisiones transplacentarias de anticuerpo fueron demostradas en 63% de las 54 madres de suero positivo.

La vacuna H. pertussis suspendida en salina fué administrada a infantes en el quinto día de vida y repetida al primer y segundo mes de edad. Con una dosis total de 50 billones H. pertussis solamente 15% de 41 infantes produjeron aglutininas en un título de 1-320 o más alto—cantidad que en niños mayores hemos concordado con inmunidad clínica. Cuando la dosis total en un segundo grupo de niños fué reducida a 100 billones H. pertussis, el título arriba mencionado fué demostrado en 25% de 145 infantes.

La respuesta serológica de infantes cuya sangre de cuerda no había contenido aglutininas no fué superior a la de los infantes con aglutininas. Asi ninguna depresión de la respuesta inmune por medio de anticuerpo adquirido transplacentariamente fué demostrable.

En un tercer grupo de 134 infantes un poco mayores de edad, la vacuna H. pertussis suspendida en salina fué administrada en un total de 80 billones células divididas en tres inyecciones mensuales. La primera inyección fué puesta de la 4a. a la 8a. semana de edad. Cuarenta y ocho por ciento de estos infantes tuvieron aglutininas en un título de 1-320 o más alto. Sin embargo, tres meses más tarde solamente 36% tenían este alto título. Las reacciones febriles generales no fueron raras y un caso probado de pertussis suave ocurrió en este grupo.

En un cuarto grupo de 151 infantes, la vacuna H. pertussis alumprecipitado fué inyectada en una dosis total de 40 billones de células divididas en tres inyecciones a intervalos de un mes. La primera inyección se puso de 4 a 8 semanas de edad. Solamente dos reacciones febriles ocurrieron, una estuvo asociada con una reacción local que no bajó. Sesenta y dos por ciento de 115 infantes, cuyos sueros fueron analizados de 4 a 8 semanas más tarde tuvieron aglutininas H. pertussis en un título de 1-320 o más alto. Doce meses más tarde 60% aún tenían estos títulos altos. Esta respuesta satisfactoria a esta edad con este producto es confirmatorio de los estudios de Sako, Treuting, Witt y Nichamin. Viene a sostener sus tésis de que la inmunización activa con vacuna alum-precipitada puede llevarse a cabo antes del sexto mes de vida.

Se describe un programa para inmunización durante el primer año de vida, incorporando la inmunización que principia a la edad de 4 a 8 semanas.

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MENINGITIS IN PREMATURE INFANTS

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THE diagnosis of meningitis in premature infants is not a common one. In a survey of the literature, only 45 recorded cases were found, of which two recovered (Table I). One recovery was reported in an infant who was born prematurely but who developed meningitis at 4½ months of age. The other recovery was in an infant reported as premature who weighed 2.4 kg. at birth. In 10 of the 45 recorded cases, bacteria were cultured from the spinal fluid; in 6 of the 10 cases, the cultures revealed gram negative bacilli.

During the 20 year period, January 1928 through December 1947, there were 12 cases of meningitis among 7,129 patients in the Sarah Morris premature station (an incidence of 1.6 cases per thousand). Of these 12 cases, spinal fluid cultures revealed Esch. coli in six, Esch. coli and pneumococcus in one, Esch. coli and K. pneumoniae in one, A. aerogenes and Esch. coli in one, pneumococcus in one, streptococcus in one, and nonhemolytic streptococcus and K. pneumoniae in one. Thus, in 6 of the 12 cases, Esch. coli was cultured from the spinal fluid; it was also found as one of two organisms in three of the remaining six cases. This is of great practical importance, particularly today, with the availability of streptomycin and more recent experience with polymyxin.[9] Esch. coli has been reported to be the commonest single cause of meningitis among full term infants. Of 42 cases of meningitis in full term infants under 5 months of age, Barron[10] found 14 caused by Esch. coli (33%). Craig[4] reported 10 cases due to Esch. coli among 21 newborn full term infants who developed meningitis; this is in contrast to the well known fact that in older infants and children the most common infecting organisms are N. intracellularis, Myco. tuberculosis, D. pneumoniae, H. influenzae, staphylococcus and streptococcus. As a cause of meningitis in older children, Esch. coli is rare.

The early diagnosis of meningitis in the premature, as in the newborn infant, is difficult. In the cases reported in this study the usually characteristic signs of the disease were often absent. Instead there were only cyanosis, fever, vomiting and perhaps icterus, all of which, and certainly any one of which, may have been due to many other causes. Nuchal resistance or rigidity was a late sign. Even bulging of the fontanelle was more often absent than present; it was found in only one of the 12 cases and was not present then until 15 days after the onset of the meningitis. Table II gives a list of the signs together with the day of illness when each was first observed. In addition, some of the infants had a shrill high pitched cry and seemed to be more irritable than normal premature infants. Table I gives the earliest signs observed by other investigators. In addition to those we noted, Craig[4] observed fine lateral nystagmus (three cases), inequality of the pupils (one case), twitching of the face (one case) and restless head movements (one case).

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TABLE I

MENINGITIS OCCURRING IN PREMATURE INFANTS AS RECORDED IN LITERATURE*

Author	Year Reported	Age at which Diagnosis Established	Birth Weight	Earliest Signs and Symptoms	Causative Organism	Therapy	Result
Koplik[1]	1916	6 wks.	Not given	Restless Bulging fontanelle Refused nourishment Vomiting Convulsions Fever Neck slightly rigid Marked spasticity of all extremities	Streptococcus		Died
Glaser[2]	1930	8 d. at autopsy	2,040 gm.	No signs or symptoms	Pneumococcus Type III	None Diagnosed postmortem	Died
Fothergill and Sweet[3]	1933	42 hrs. at autopsy	2,400 gm.	Cyanosis Icterus, intense Pneumonia	Pneumococcus	None Diagnosed postmortem	Died
Fothergill and Sweet[3]	1933	10 d.	Not given	Jaundice Apathy Refusal of food "Instability of temperature" Full fontanelle	Gram negative bacillus either A. faecalis group or Flavus group	"Chemical and serologic"	Died
Fothergill and Sweet[3]	1933	12 d. at autopsy	Not given	Vomiting Jaundice Fever Convulsions Bulging fontanelle	Esch. acidi lactici	None Diagnosed postmortem	Died
Craig[4]	1936	13 d.	Approx. 1,400 gm.	Aural discharge—Esch. coli Anorexia Ocular signs (inequality of pupils, fine lateral nystagmus) "Spongey" fontanelle Twitching of face Anuria	Esch. coli	Not mentioned	Died
Craig[4]	1936	10 d.	Approx. 1,900 gm.	"Spongey" fontanelle Anuria Nystagmus Fever	Esch. coli	Not mentioned	Died
Craig[4]	1936	18 d.	1,700 gm.	Failure to gain weight "Spongey" fontanelle Nystagmus Restless head movements Twitching of extremities Ulcerative stomatitis	Streptococcus	Not mentioned	Died
Kutscher[5]	1937	4½ mos.	Not given	Rigid spine Stiff neck Fever (40° C.) Refused nourishment "Muscular soreness" Moderate opisthotonus	A. bookeri	None	Recovery
Shulman and Johnson[6]	1944	18 d.	2,400 gm.	Jaundice Discharging eyes Weakness Head retracted High pitched cry Persistent weight loss Fever	Proteolytic Gram negative bacillus	Sulfathiazole, orally and transfusions	Recovery

* In addition to those noted in this table, the following cases were reported as indicated: Cruickshank,[7] 14 cases in 1930; Hess[8] et al., 10 cases in 1934, and Craig,[4] 11 cases in addition to those in this table in 1936. However there were insufficient details to include them in this table.

It is apparent that if a premature infant develops fever, cyanosis and vomiting, the possibility of meningitis should be considered. The absence of nuchal rigidity, a bulging fontanelle or a positive Kernig's sign is not sufficient evidence on which to rule out such a possibility.

Of the 12 cases reported in this series, all but one died. The case of the patient who survived is reported in detail below. It was a premature infant weighing less than 1,000 gm. who recovered from an Esch. coli meningitis following administration of streptomycin.

Case Report

C. A. D., a twin white female premature infant, was born in another hospital. The other twin died immediately after birth from an undetermined cause. When 2 days old, patient was admitted to the ward service of the Premature Station, Sarah Morris Hospital. Wt. at this time was 965 gm. She

TABLE II

Signs Accompanying Meningitis in Premature Infants

Sign	No. of Cases	Day of Illness When First Observed
Cyanosis	12	1–4
Fever	11	1–4
Vomiting	10	1–8
Icterus	7	1–3
Rigidity	4	1–8
Edema	2	4–5
Convulsions	2	1
Nuchal rigidity	1	15
Bulging fontanelle	1	15
Diarrhea	1	2

was in poor condition, having a weak spontaneous cry and a small bruise on her right lower leg. She was slightly cyanotic when not given oxygen by inhalation. When 4 days old, she began to vomit a little after each feeding and her face and hands twitched slightly. Following this she improved and had no further symptoms until she was 20 days old. At this time she had gained back to 970 gm. from a low of 880 gm. when she was 5 days old. At 20 days of age, she was noted to be listless, took her feedings poorly and vomited. The following day she was apathetic, cried when touched and vomited some greenish material on several occasions. On her 21st day, temperature at 8:00 a.m. was 39.7°, but she was afebrile the rest of the day. Skin became pale, icteric and firm. The next day her extremities were somewhat rigid. A tentative diagnosis of pneumonia was made and she was given crystalline sodium penicillin G 10,000 u. in saline intramuscularly every 3 hrs. She had no more fever and appeared to recover so rapidly that after 4 days the penicillin was stopped. She weighed 930 gm. at this time after having gone down to 840 gm. during this acute episode. However, 4 days later, when she was 28 days old, she again appeared acutely ill: she was irritable, body was slightly rigid and skin was slightly icteric. She cried when touched. The day before she had taken her feedings well, but now she had to be fed by gavage. Although afebrile at that time, temperature rose the next day to 41.3° within a period of a few hrs. Eyelids began to twitch and extremities were again spastic. Spinal tap, which yielded a few drops of bloody fluid, was done. This fluid showed many erythrocytes and some polymorphonuclear cells. The infant improved without therapy and gained weight steadily; on her 30th hospital day she weighed 995 gm. At this time, however, she developed marked bulging and tenseness of her fontanelles as well as marked rigidity of her body and stiffness of her neck. She was afebrile but irritable and pale. A fontanelle puncture yielded 10 cc. of bloody cloudy fluid. A direct smear revealed many gram negative bacilli. Sodium penicillin G in saline 5,000 Oxford u. was given intramuscularly every 3 hrs. and sodium sulfadiazine 0.25 gm.

was given subcutaneously every 12 hrs. at this time. Patient improved somewhat overnight and the fontanelle became less tense. Another fontanelle tap was done and 10 cc. of fluid were withdrawn again. Cultures of both fluids obtained from the fontanelle revealed organisms which were identified as Esch. coli. A slight right facial paralysis developed the following day and she continued to vomit occasionally for from 2 to 3 wks. On the infant's 31st hospital day, her abdomen became distended and she began to vomit green material again in large amounts. On her 35th hospital day, spinal fluid still revealed Esch. coli on culture and there was little clinical improvement. At this time, penicillin and the sulfonamide were discontinued and streptomycin was started. The latter drug, obtained through the courtesy of Dr. Chester S. Keefer, who also recommended the dosages, was given as follows: 1 dose of streptomycin 0.025 gm. in 1 cc. of distilled water was injected intrathecally; 0.125 gm. in 0.5 cc. was given intramuscularly every 3 hrs. Some improvement in the infant's general condition was noted within 24 hrs. The intramuscular streptomycin was continued for a total of 7 days. Three days after this therapy was started, the spinal fluid was sterile for the 1st time but showed 450 white cells; protein was 600 mg./100 cc.; glucose was 15 mg./100 cc. During this entire episode the infant took breast milk fairly well and continued to gain, weighing 1,060 gm. on her 41st hospital day. There was still some fullness of her anterior fontanelle and she vomited occasionally. Circumference of her head was 30 cm. and of her chest 22 cm. Thereafter, her course was uneventful and she was discharged on her 100th hospital day (aged 102 days) weighing 2,100 gm. Physical examination at the time of discharge revealed no abnormalities. Head circumference was 35.5 cm. and chest 30 cm. Length was 43 cm.

A complete examination at 2 yrs. of age, including neurologic and psychologic testing, revealed that her development was equivalent to the average normal 2 yr. old child.

Discussion

The incidence of meningitis among premature infants over a 20 year period was 1.6 per thousand admissions to the Premature Station. Of 12 premature infants with meningitis, six cases were found to be due to Esch. coli, and this organism was found as one of two infecting bacteria in three of the remaining six cases. In view of the fact that streptomycin is usually effective against gram negative organisms whereas penicillin ordinarily is not effective and the sulfonamides are generally less effective, and since a majority of cases of meningitis in premature infants is caused by gram negative organisms, streptomycin should be given to newborn and premature infants with meningitis unless it can be promptly determined that the meningitis is due to other than a gram negative organism. Inasmuch as there may be synergistic action between the sulfonamides and streptomycin[11] against these organisms, and since the mortality rate is so high, it may be wise to administer both drugs to these cases. Recent work shows that polymyxin B (aerosporin) is weight for weight about 200 to 400 times as effective against Esch. coli as is streptomycin. It is, therefore, possible that this new antibiotic may be found to be the drug of choice for these infections.[9, 12]

The early diagnosis of meningitis in premature infants is difficult. The appearance of fever, cyanosis and vomiting may be the only signs. Fever in a premature infant, particularly without evidence of another etiology, should lead one to consider meningitis. Nuchal rigidity, bulging fontanelle and convulsions are usually absent. When they were present in this series, nuchal rigidity and bulging of the fontanelle were late signs.

Summary

A review of the literature on the subject of meningitis in premature infants revealed 45 cases. In 10 of these cases from which bacterial agents were cultured, six showed a gram negative bacillus.

Twelve additional cases are added in this study and Esch. coli was cultured from the spinal fluid of nine (with another organism in three of the nine cases).

The symptoms and signs of meningitis in premature infants are discussed.

No reports have been found in the literature of recovery from meningitis in premature infants weighing less than 2,500 gm. The course and treatment of a premature infant who weighed less than 1,000 gm. and who recovered from an Esch. coli meningitis is described in detail.

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Spanish Abstract

Meningitis en Infantes Prematuros

Una revista de la literatura sobre el sujeto de meningitis en infantes prematuros reveló 45 casos. En 10 de estos casos, de los cuales se hizo el cultivo de los agents bactéricos, seis mostraron un baccilo negativo.

Se agregaron doce casos a este estudio y Esch. coli fué cultivado del flúido espinal de nueve (con otro organismo en tres de los nueve casos).

Los síntomas y señas de meningitis en infantes prematuros fueron tratados.

No se han encontrado datos en la literatura del restablecimiento de la meningitis en infantes prematuros que pesan 2,500 gm. o menos. Se describe en detalle el curso y tratamiento de un infante prematuro que pesaba menos de 1,000 gm. y que se restableció de una meningitis Esch. coli.

29th Street and Ellis Avenue

RELATION OF PLASMA PROTEINS TO BIRTH WEIGHT, MULTIPLE BIRTHS AND EDEMA IN THE NEWBORN

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THE concentration of plasma proteins in the blood of full term and premature newborn infants has been studied by several authors. A complete bibliography was given in a recent report on this subject from this clinic.[1] There is general consensus that the plasma of these infants contains less protein than is found in that of older children and adults. This is due to lower values for both the albumin and the globulin fractions, though the greater proportional difference is in the globulin fraction. It is generally agreed also that the plasma proteins occur in lower concentrations in premature infants than in infants born at term. There have been, however, only two studies[1, 2] in which there has been an attempt to correlate the degree of relative protein deficiency with the degree of maturity. In order to clarify this question further, a study has been made of the plasma protein concentration in a large number of newborn infants with a wide range in birth weight. Since the gestational history is notoriously inaccurate in patients seen in this hospital, the degree of prematurity has been determined solely on the basis of birth weight.

Early in the study it was noted that twin infants seemed to have lower concentrations of plasma proteins than did singly born infants of comparable birth weight. Therefore, the plasma proteins of twin infants have been studied as a separate problem. Ten newborn infants with edema were encountered in this study. The results of a study of their plasma proteins are included in this report.

SUBJECTS

The subjects of this study were in the nurseries for premature and newborn infants of the Gallinger Municipal Hospital. Two hundred and seventy infants were studied in all. Of these, 135 were apparently healthy premature infants, 88 were normal full term infants, 32 were twin infants and 10 were infants with edema. Blood was drawn for study within 48 hrs. after birth in the case of premature infants and between 12 and 36 hrs. in the case of full term infants. Obviously dehydrated infants or infants with known disease (except edema of the newborn) were not chosen. Blood was drawn at approximately the same time each day and at the same time in relation to feeding.

METHODS

Plasma proteins were determined by the Greenberg[3] method, using the Kingsley[4] procedure for separating albumin from globulin, as reported previously from this laboratory.[1] An Evelyn photoelectric colorimeter was used. Total protein, albumin and globulin values were determined separately and specimens discarded if the sum of the albumin and globulin did not come within 7% of the separately determined value for total protein. The majority of determinations agreed within 5%. Accuracy of the colorimetric results was determined by frequent checks made on pooled specimens using the micro-Keldjahl procedure. The results obtained by using both methods were in close agreement. The values obtained here are lower than those previously reported from this laboratory.[1] The previous values were obtained by using a tyrosine standard purchased commercially. This tyrosine

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TABLE I

BLOOD PLASMA PROTEIN LEVELS IN NEWBORN PREMATURE AND NEWBORN FULL TERM INFANTS

Wt. (in gm.)	No. Cases	Total Protein (gm./100 cc.)		Albumin (gm./100 cc.)		Globulin (gm./100 cc.)	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
1,000 to 1,499	17	4.66	±0.50	3.14	±0.39	1.38	±0.22
1,500 to 1,999	77	5.19	±0.79	3.46	±0.56	1.70	±0.28
2,000 to 2,499	36	5.40	±0.67	3.50	±0.50	1.90	±0.33
2,500 to 2,999	20	5.77	±0.72	3.85	±0.73	1.90	±0.30
3,000 to 3,499	25	5.64	±0.80	3.76	±0.67	1.87	±0.45
3,500 to 3,999	23	5.49	±0.42	3.52	±0.44	1.87	±0.35
4,000 and above	20	5.57	±0.61	3.54	±0.41	1.87	±0.32
Total Premature Infants 1,000 to 2,499 gm.	130	5.10	±0.71	3.40	±0.55	1.7	±0.33
Total Full Term Infants 2,500 gm. and above	88	5.6	±0.66	3.7	±0.58	1.9	±0.30

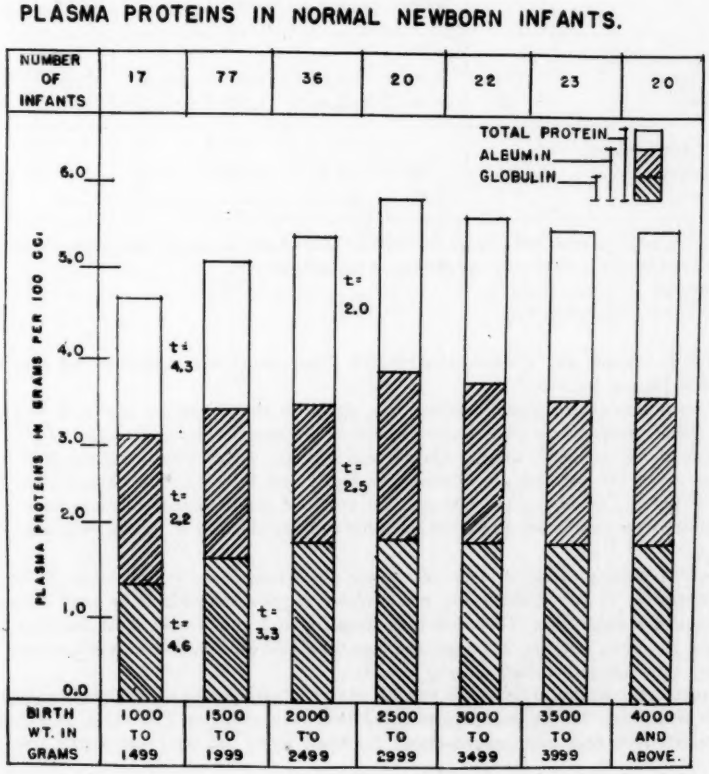

FIG. 1.

was labelled "C.P." The present values were obtained by using a tyrosine standard prepared in a local biochemical laboratory from enzymatically hydrolyzed casein and was twice recrystallized. A direct comparison of the 2 standards by the technic employed in this study gave protein values that were approximately 15% lower with the standard used in the present study. This may account for the lower values for total protein reported herein. There are other differences in the albumin-globulin fractions which are unexplained and which may be due to inherent difficulties with the salt-precipitation technic of fractionation.

Results

The singly born infants were divided into 7 groups according to birth weight. Each group had a range of 500 gm., beginning with 1,000 to 1,499 gm. and ending with a group weighing 4,000 gm. and above.

The results are given in Table I and Figure 1. The mean plasma protein values for premature infants were found to be significantly lower than those of full term infants ($t = 5$, 2.8 and 4 for

TABLE II

Comparison of Blood Plasma Protein Levels of Newborn Single Infants with Those of Newborn Twin Infants

	No. Cases	Total Protein (gm./100 cc.)		Albumin (gm./100 cc.)		Globulin (gm./100 cc.)	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Premature Infants							
Single	130	5.10	±0.71	3.40	±0.55	1.70	±0.33
Twin	25	4.80	±0.68	3.10	±0.56	1.60	±0.28
Full Term Infants							
Single	88	5.60	±0.66	3.70	±0.58	1.90	±0.30
Twin	7	4.80	±0.41	3.20	±0.77	1.60	±0.32

Values for total proteins and protein fractions in twin infants are lower than those found in single infants. Even in such a small series all differences are significant.*

* Premature $t=6.0, 2.63, 3.03$.
Full Term $t=3.2, 2.5, 2.5$.

total protein, albumin and globulin, respectively). These values were essentially the same as those obtained by Darrow and Cary.[8]

The mean albumin and globulin values show significant and progressive rises with weight in the smaller infants. Both plasma albumin and globulin values increase with birth weight up to 2,499 gm. In infants above this birth weight, albumin and globulin values show relatively little variation. Globulin values are remarkably consistent (see Fig. 1 and Table I). The albumin value shows a further increase in infants up to 2,999 gm., but this is of questionable significance since the values obtained in larger infants are essentially the same as those obtained in infants weighing 2,000 and 2,499 gm.

Mean values for all proteins in the plasma are significantly lower in twin infants (Table II). A sufficient number of twin patients was not available to make comparisons by small increments of weight with the singly born. They have been compared in 2 groups only, those weighing less than 2,500 gm. and those weighing 2,500 gm. and over. The differences in protein levels are striking, and significant even with such a small group of patients.

An unexpected feature in this study was the degree of variation in protein levels encountered in pairs of twins. Both infants were studied in 14 twin deliveries (see Table III). Binovular twins varied widely from each other and frequently the larger infant had the lower protein level. Only 2

of these pairs of twins were monovular, too small a number from which to draw conclusions. The variations may be due in part to inherent errors present in all methods of determining plasma protein which utilize salt-precipation, and in part to dehydration and changing blood volume after birth. However, the variations seem to be too wide to be entirely accounted for in this manner.

Plasma protein values of 10 infants born with edema are presented in Table IV. The 2 full term

TABLE III

PLASMA PROTEIN LEVELS IN TWIN INFANTS

	Wt. in gm.	Total Protein (gm./100 cc.)	Albumin (gm./100 cc.)	Globulin (gm./100 cc.)
Monovular Twins				
I	1,736	5.10	3.29	1.67
	1,821	4.54	3.09	1.59
II	1,480	4.54	3.23	1.34
	1,562	4.72	3.00	1.58
Binovular Twins				
I	2,197	4.96	3.49	1.55
	2,325	6.19	4.06	1.95
II	2,580	4.15	3.09	1.15
	2,787	4.82	3.26	1.72
III	2,154	5.31	3.64	1.94
	2,381	4.96	3.25	1.66
IV	2,445	4.72	3.03	1.46
	2,811	5.10	3.03	1.83
V	2,763	4.19	2.89	1.43
	2,910	4.61	3.06	1.64
VI	1,530	3.94	2.27	1.50
	1,714	4.69	3.02	1.69
VII	1,729	4.35	3.17	1.06
	2,502	5.71	3.61	2.08
VIII	2,239	5.63	3.58	2.13
	3,152	5.11	3.58	1.67
IX	2,175	4.03	2.55	1.46
	2,231	4.68	3.06	1.67
X	2,005	3.68	2.23	1.25
	2,069	5.49	3.36	1.97
XI	2,168	3.89	2.22	1.40
	2,218	3.84	2.22	1.53
XII	2,325	6.16	4.23	1.73
	2,552	5.66	3.38	2.18

TABLE IV

PLASMA PROTEIN LEVELS IN EDEMATOUS NEWBORN INFANTS

Case No.	Wt. in gm.	Total Protein gm./100 cc.	Albumin gm./100 cc.	Globulin gm./100 cc.	Comment
1	3,344	5.92	3.24	2.53	Globulin high
2	2,693	4.95	2.83	2.01	Albumin slightly low
3	2,410	4.99	3.61	1.54	Normal
4	2,291	5.71	3.55	1.97	Normal
5	2,069	5.10	3.29	1.68	Normal
6	2,012	4.97	3.54	1.44	Normal
7	1,814	6.32	4.13	2.01	Normal
8	1,786	4.88	3.49	1.42	Normal
9	1,700	5.36	3.76	1.47	Normal
10	1,133	4.96	3.88	1.30	Normal

infants varied from the mean values of their weight group in that 1 infant (Case 1) had a high globulin and the other (Case 2), a slightly lowered albumin. All 8 premature infants had values which were well within normal limits for infants of their weight.

DISCUSSION

The study of plasma protein levels is important from the point of view of immunity and of nutrition. According to the data obtained in this study, the levels of albumin and globulin rise as the infant approaches maturity. After maturity is reached, these levels remain relatively constant.

While this work was being done, a similar study was published by Rimington and Bickford in England.[2] Determinations of albumin and globulin were made on maternal and cord blood in 38 instances. They reported that fetal albumin and globulin increased with the length of gestation. The results in the study presented here are similar, although the degree of prematurity was based on birth weight and infant blood was used.

There is a feeling among some investigators in the field that infants are able to synthesize their own proteins independently of the mother.[6] The work reported here, it is believed, lends support to this belief since twin infants show levels which vary from each other. This may indicate that such infants vary in their power to synthesize proteins and, from an immunologic point of view, may vary in their ability to produce antibodies.

A premature infant on whom serial plasma proteins were being done illustrates the ability of a young premature infant (1,558 gm.) to synthesize globulin. The mother had miliary tuberculosis and the infant showed signs of congenital tuberculosis at the age of 8 weeks. The infant responded favorably to treatment with streptomycin. (This case is to be reported in detail by Amick and Monaco.[7]) The globulin value rose steadily from a level of 1.26 gm./100 cc. blood at 48 hours to 1.70 gm. at 6 weeks, 2.33 gm. at 8 weeks and 2.76 gm. at 10 weeks. At the age of four months, with apparent recovery, the globulin measured 1.8 gm./100 cc. The rise in globulin was timed with infection and the fall with apparent recovery.

Longsworth and his colleagues,[8] using electrophoresis, showed that the globulin fraction of cord blood consisted mainly of γ-globulin in contrast to maternal globulin in which α- and β-globulin predominated. It would be most interesting if electrophoretic analysis

could be done on the blood of premature infants of varying degrees of maturity to determine which of the globulin fractions increase with increasing maturity of the infant.

The normal protein levels found in infants born with edema support the current conception that this phenomenon is largely attributable to a retention of electrolyte[9, 10] rather than to hypoalbuminemia in infants without liver disease. With subsidence of the edema, the protein levels remained essentially the same.

Conclusions

The concentration of total protein, albumin and globulin in the plasma increase with increasing birth weight in premature infants. These values are relatively stable and independent of birth weight in mature newborn infants. Infants born as twins have lower plasma protein values than do singly born infants of corresponding birth weight. The plasma protein values of twins may vary widely one from the other. This finding supports the theory that plasma proteins in the infant are produced and regulated independently of the mother. Infants born with edema may have essentially normal plasma protein values.

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Spanish Abstract

Relación de las Proteínas de la Sangre con el Peso de Nacimiento, Partos Múltiples y Edema en el Recién Nacido

Se hicieron determinaciones de albumina de plasma, globulina y proteína total en 270 infantes recién nacidos durante las primeras 48 horas de vida. Estos incluyeron infantes normales cuyo peso de nacimiento era de 1000 gm. a un poco más de 4000 gm., infantes gemelos y unos cuantos infantes con edema. Las concentraciones de albumina media, globulina y proteína total aumentaron con el aumento de peso del nacimiento hasta madurez (2500 gm.), después permanecieron relativamente constantes, sin referencia al peso de nacimiento. Hubo considerable variación en las concentraciones de proteína de "siblings" gemelos. Se encontró que los infantes con edema tenían concentraciones de proteína de plasma que eran dentro de la extensión normal para pacientes de su tamaño.

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DIAGNOSTIC TESTS FOR TOXOPLASMOSIS

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ACUTE, chronic and latent toxoplasmosis are known to occur throughout the United States and in several foreign countries, but the accurate diagnosis of the disease in its various forms presents many difficulties. The isolation of the Toxoplasma from man has been accomplished in only a few instances.[1-8] The true incidence of the disease is almost unknown. Rabbit neutralization and complement fixation tests have been of distinct value, but their use requires a well equipped laboratory and many animals, which make the cost unduly high. Recently the slide neutralization test[9] and the human skin test[8] have been added to our armamentarium for diagnosis of this disease. A comparative study of all of these diagnostic tests was undertaken with the view of determining their relative reliability.

METHODS AND MATERIALS

Rabbit Neutralization Test.—We have used essentially the same technic for this test as that described by Sabin[10] except that we have substituted normal saline solution for the Tyrode's solution which he used as the diluent. Our final dilutions of Toxoplasma have been 1:50, 1:250, 1:1,250 and 1:5,000 instead of 1:20, 1:100, 1:1,000 and 1:10,000. Some of the sera were tested fresh but most were tested after storage in a CO_2 refrigerator for varying periods up to several weeks. Our criteria for a positive neutralization against the Toxoplasma are the same as those used by Sabin.

Complement Fixation Test.—This test now employed in this laboratory (modified by one of us, M. C.) is slightly different from that first reported by Warren and Sabin.[11] The antigen used is derived from a pool of mouse peritoneal exudate containing large numbers of Toxoplasma. The pool of peritoneal fluid is frozen and thawed 5 times in order to kill and break up the organism. The solid material is then removed by centrifugation in an angle head centrifuge. The supernatant fluid constitutes the antigen.

Antigen undiluted and in dilutions of 1:5, 1:10, 1:20, 1:40, 1:80 and 1:160 are titrated against a known positive antiserum in 5 2-fold dilutions which include the previously established endpoint for the antiserum. The antigen is then used in the test in the highest dilution which gives a 4+ fixation of complement with the highest serum dilution. Antigens are usually diluted from 1:20 to 1:80. A pool of guinea pig serum frozen in CO_2 is used as complement. Two units of antisheep cell hemolysin are employed in the test. Complement and hemolysin titrations are set up for each group of tests.

Two-fold dilutions of the patients' serum, 1:2, 1:4, 1:8 and 1:16, are made up in 0.2 ml. amounts with physiologic saline. To each serum dilution, 0.2 ml. of antigen is added. After an interval of 10 min., 0.2 ml. of complement diluted to contain 2 u. is added, and the mixture is allowed to remain in the icebox for 15 to 18 hrs. After the mixture is warmed for 10 min. in a water bath at 37°C., 0.4 ml. of a hemolytic mixture, consisting

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of equal parts hemolysin (diluted to contain 2 u./0.2 ml.) and 2% suspension of sheep red cells is added to it before it is shaken and placed in a water bath at 37°C. The usual controls are included with the tests which are read 10 min. after the controls clear.

Skin Test.—An antigen obtained from Dr. J. K. Frenkel of San Francisco, prepared from infected mouse peritoneal exudate according to a method described by him,[8] was used in the 1st 20 subjects tested with toxoplasmin skin material. The next 10 subjects were tested with both the Frenkel antigen and 1 prepared by ourselves. The remaining 118 subjects were tested with our antigen only. This antigen was prepared by inoculating 3 young Swiss mice each with 0.2 cc. of a 1:5 suspension in saline of peritoneal exudate obtained from a strain maintained by continuous intraperitoneal passage. After 3 days the mice were killed, the abdominal skin laid back and the peritoneal exudate (about 2.2 cc.) obtained by sterile aspiration with a syringe and a #22 needle. This peritoneal exudate was diluted with normal saline 1:5. The diluted peritoneal exudate was frozen and thawed 3 times, and then aqueous merthiolate was added to make a final dilution of 1 to 10,000 of merthiolate. This solution was centrifuged at 3,000 r.p.m. for 15 min. following which the supernatant fluid was drawn off and saved. The procedure was repeated a 2nd time to assure removal of all solid material and the final supernatant fluid was stored in a CO_2 refrigerator until ready for final dilution. As a special precaution, some of the final supernatant fluid was inoculated into mice, rabbits, guinea pigs and ordinary bacteriologic culture media before being used in human testing. No growth on the culture media or reactions of any type in the animals mentioned was observed after 1 mo.

The testing procedure employed in this study of human hypersensitivity to the toxoplasma antigen consisted of injecting 0.1 cc. of a 1:500 dilution of the toxoplasmin intradermally on the forearm of the patient. The area was examined after 24 and 48 hrs. for swelling and redness; a test was regarded as positive when any swelling or redness existed that was larger than the original area of injection (0.5 cm.) at the end of the 48 hrs.

Slide Neutralization Test.—This new method, developed by Sabin and Feldman,[9] was found by them to give results which correlated closely with those obtained with the rabbit neutralization test. We have likewise made comparative studies of sera with the slide test and have found it to be quicker and easier to perform than the other. Antibody titers can be determined more readily by its use. This test has the further advantage that positive sera, which have become inactivated either purposefully or accidentally as a result of improper storage, can be reactivated by adding serum containing the "accessory factor."

The test consists essentially of mixing equal parts of a dilution of peritoneal exudate (obtained from mice infected with Toxoplasma inoculated intraperitoneally) and the serum to be tested, incubating the mixture in a water bath at 37°C. for 1 hr., placing a drop of the mixture which has been incubated on a slide, adding a drop of specially prepared saturated alcoholic methylene blue (pH11) and mixing. A cover slip is placed over the combination and the preparation is examined under the high power of the microscope. If the substances are properly mixed and in the right dilutions, there will be 10 to 20 Toxoplasma evenly distributed throughout the field. In the absence of antibody in the serum tested, 90 to 100% of the Toxoplasma take up the dye and appear stained. In the presence of antibody in the serum tested, less than 50% of the Toxoplasma take up the dye. If the serum to be tested has been stored improperly or the antibody titer is to be determined, the Toxoplasma must be diluted with serum that is known to reactivate negative tests to positive tests and yet does not contain toxoplasmic antibody itself. In

TABLE I

RESULTS OF RABBIT, SLIDE AND COMPLEMENT FIXATION TESTS IN 53 PATIENTS

No.	Name	Age	Diagnosis	Rabbit Neutralization	Slide Neutralization	Complement Fixation	Remarks
1	B.B.	0	Newborn	−	−	−	
2	B.H.	0	Newborn	−	−	−	
3	B.W.	0	Newborn	−	−	−	
4	B.B.	0	Newborn	−	−	1:4	
5	B.S.	0	Newborn	+	+	−	
6	B.W.	0	Newborn	+	+	AC	
7	D.G.	2 mos.	Choroiditis	−	+	1:128	Slide test positive with activator.
8	B.B.	2 mos.	Toxoplasmosis	+	+	1:128	Slide test positive in prozone.
9	I.V.	...	...	+	+	−	
10	S.P.	...	...	+	+	−	
11	G.J.	2 mos.	Jaundice	−	−	−	
12	D.S.	3 mos.	Hydrocephalus	−	+	−	Slide test positive with activator.
13	A.C.	8 mos.	Toxoplasmosis	+	+	−	
14	J.N.	1	Convulsions	−	−	−	
15	J.J.	2	Rheumatoid	−	−	−	
16	S.B.	2	Toxoplasmosis	−	+	1:64	Slide test positive with activator.
17	D.W.	3	Rheumatic fever	−	−	−	
18	R.G.	5	Normal	−	−	−	Sibling has toxoplasmosis.
19	J.S.	5	Rheumatoid	+	+	−	
20	M.H.	5	Rheumatic fever	−	−	AC	
21	D.W.	5	Rheumatoid	−	−	AC	
22	S.R.	5	Rheumatic fever	−	−	−	
23	M.K.	5	Erythema exudativum	−	−	−	
24	S.K.	5	Rheumatoid	+	+	−	Previous CF tests elevated to 1:64
25	C.K.	5	Rheumatic fever	−	−	−	
26	D.M.	5	Toxoplasmosis	+	+	1:4	
27	E.O.	6	Convulsions	−	−	−	
28	C.V.	7	Hydrocephalus	+	+	1:4	
29	F.H.	9	Rheumatic fever	−	−	−	
30	G.S.	10	Convulsions	−	+	−	Slide test positive with activator.
31	M.B.	12	Brain tumor	+	+	−	
32	H.O.	14	Rheumatic fever	+	+	−	
33	J.K.	21	Rheumatoid	−	+	−	Slide test positive with activator.
34	J.G.	22	Normal	+	+	−	
35	M.B.	23	Normal	−	−	−	Mother of Patient 1.
36	F.B.	24	Normal	−	−	−	Mother of Patient 4.
37	M.Z.	24	Pregnant	−	−	AC	
38	M.H.	25	Normal	−	−	−	
39	M.T.	26	Pregnant	−	−	AC	
40	M.H.	28	Pregnant	−	−	AC	
41	M.H.	28	Father	−	−	−	
42	M.H.	30	Normal	−	+	1:4	Slide test positive with activator.
43	B.B.	32	Normal	−	+	−	Slide test positive with activator.
44	M.P.	35	Normal	+	+	−	Mother of Patient 10.
45	M.G.	35	Normal	−	−	1:16	Mother of Patient 7.
46	M.K.	37	Pregnant	−	−	AC	
47	M.B.	38	Normal	+	+	1:32	Slide test positive in prozone. Mother of Patient 8.
48	M.V.	38	Normal	+	+	−	Mother of Patient 9.
49	M.H.	40	Chorioretinitis	+	+	1:16	
50	M.B.	43	Normal	+	+	1:64	Mother of Patient 16.
51	M.W.	28	Normal	−	−	−	Mother of Patient 3.
52	M.M.	35	Normal	+	+	1:32	Mother of Patient 26.
53	M.L.	43	Normal	−	−	−	Mother of patient with acquired toxoplasmosis.

+ Positive.
− Negative.
... Information not available.
AC Serum Anti-complementary.

determining the actual antibody titer, various dilutions of the serum to be tested are mixed with the Toxoplasma-activator (serum) mixture. In all instances the tests are read within 1 hr. after completion of the incubation; those tests not being read are kept at 4°C. For further details of the technics used in performing the tests and for the method of preparation of the dye, the reader is referred to the work of Sabin and Feldman.[9]

Most of the patients used for evaluating these tests were seen by one of us (F. H. A.). A few of the sera tested were submitted to the Minnesota State Department of Health by doctors throughout the State of Minnesota; some specimens were received from outside the state. Nearly all the specimens showing positive reactions were from patients in the pediatric wards of the University of Minnesota Hospitals. Serum samples for the study on unselected ward patients were also drawn from the latter source. The investigations on separate groups of hydrocephalic, microcephalic, cerebrospastic and mongoloid patients were done at the Minnesota School and Colony for the mentally defective through the courtesy of Dr. E. J. Engberg, Superintendent.

Results

Correlation of the Rabbit, Slide and Complement Fixation Tests.—At the beginning of this study only the 3 tests were used as most of the sera were already on hand and it was not possible for the patients to return for skin testing. Specimens from 53 patients were tested by the rabbit, slide and complement fixation methods. The results of these tests in the individual patients together with the age and diagnosis of each are presented in Table I. Nineteen sera showed a positive neutralization in both the rabbit and slide tests, while only 10 sera reacted to the complement fixation test. When activator serum was added to the mixture as described under the method of the slide neutralization technic, 7 additional sera gave a positive test.

Correlation of the Rabbit, Slide, Complement Fixation and Skin Tests.—A total of 143 patients were studied with the 4 tests. The sera of 26 were positive by the rabbit neutralization, 33 sera were positive by the slide test, 11 were positive to the complement fixation, 29 had a positive skin test and 107 failed to react to any of the 4 tests.

As can be seen in Table II, in 7 instances the slide test was positive while the rabbit test was negative. In 2 instances, the slide test was the only 1 giving a positive test, and in 1 instance the complement fixation test was the only test that was positive. The skin test was negative in 3 instances, when 2 or more of the other tests were positive.

Results of Skin Testing.—The skin test was applied to 188 patients to determine its usefulness in random sampling and to determine the incidence of positive tests in certain disease conditions. In 40 unselected pediatric ward patients, suffering from various functional and organic diseases, 4 had a positive skin test. Among 148 patients tested at the Minnesota School and Colony, 1 of 25 hydrocephalics was positive; 5 of 52 mongolian idiots were positive; 1 of 29 microcephalics was positive, but none of 42 cerebrospastics were positive. Taken as a group, the 188 patients showed 11% positive toxoplasmin skin tests.

Reversal of Positive Tests.—In the course of this 1948 study, 6 patients whose sera had shown a definitely positive rabbit neutralization test in 1946 and 1947 (and in 2 instances also a positive complement fixation test) were asked to return for the 4 tests (rabbit, slide, complement fixation and skin). In 5 of the 6 patients, the 4 tests were repeatedly found to be negative. In 1 patient only, the rabbit test was repeated and it was negative (see Table III).

TABLE II

RESULTS OF RABBIT, SLIDE, COMPLEMENT FIXATION AND SKIN TESTS IN PATIENTS WHERE ONE OR MORE TESTS WERE POSITIVE

No.	Name	Age	Sex	Diagnosis	Rabbit Neutralization	Slide Neutralization	Complement Fixation	Skin Test	Remarks
1	G.C.	1	M	Toxoplasmosis	+	+	1:512	+	
2	M.C.	30	F	Normal	+	+	1:8	+	Mother of 1
3	F.C.	32	M	Normal	+	+	1:2	+	Father of 1
4	C.G.	15	F	Toxoplasmosis	+	+	1:32	+	
5	M.G.	48	F	Normal	+	+	−	+	Mother of 4
6	S.K.	5	F	Rheumatoid	+	+	1:16	−	
7	C.L.	22	M	Macular degen.	+	+	1:14	+	
8	E.L.	16	M	Macular degen.	+	+	−	+	
9	E.L.	45	F	Normal	+	+	1:12	+	Mother of 7
10	M.H.	28	F	Normal	+	+	−	+	
11	T.S.	28	M	Normal	+	+	−	+	
12	V.K.	31	M	Normal	−	+	−	+	
13	R.H.	6	M	Eczema	+	+	1:16	−	Slide test positive in prozone.
14	T.Z.	13	M	Burn	+	+	−	+	
15	L.S.	8	M	Cataracts	+	+	−	+	
16	D.B.	9	M	Diabetes	+	+	−	+	
17	R.B.	9	M	Poliomyelitis	+	+	−	+	
18	J.L.	9	M	Toxoplasmosis	+	+	−	+	
19	G.V.	5	F	Normal	+	+	1:2	+	
20	H.H.	25	F	Pregnant	−	+	−	+	
21	H.R.	21	F	Pregnant	+	+	−	+	
22	H.N.	20	F	Pregnant	+	+	AC	+	
23	H.K.	15	F	Pregnant	+	+	−	+	
24	K.W.	24	F	Pregnant	+	+	−	+	
25	P.R.	13	F	Pregnant	+	+	−	+	
26	J.L.	13	F	Pregnant	+	+	−	−	
27	M.K.	39	F	Microcephalus	−	+	−	+	
28	R.H.	17	M	Mongolism	−	+	−	+	
29	G.D.	18	M	Mongolism	+	+	1:8	+	
30	E.D.	26	F	Mongolism	−	+	−	−	
31	L.E.	14	F	Mongolism	+	+	−	+	
32	K.M.	14	F	Mongolism	−	−	−	+	
33	V.E.	26	M	Hydrocephalus	−	−	−	+	
34	M.H.	2 mos.	F	Diarrhea	−	+	−	−	
35	J.C.	6 mos.	M	Pneumonitis	−	+	−	−	
36	B.T.	2 mos.	M	Jaundice	−	−	1:8	−	

Prozone Phenomenon.—In 3 instances (Patients 8 and 47 of Table I and 13 of Table II) the slide test was negative when the patient's serum was used undiluted. Since 1 or more of the other tests were positive in these patients, a prozone effect was suspected and tested for. Patients 8 and 47 of Table I were baby and mother, respectively, in whom the diagnosis of toxoplasmosis was considered probable. In the case of these patients, the sera gave a positive test in a dilution of 1:1,024. Unfortunately, not enough serum was available to determine the end point of these reactions.

DISCUSSION

Frenkel[8] has discussed the disadvantages of both the rabbit neutralization test and the complement fixation test for toxoplasmosis. He expressed the need for a test which would be less costly, simpler and more rapid in performance. He recommended the skin test with toxoplasmin as fulfilling these requirements. His studies indicate that while the skin test with toxoplasmin antigen does not give a 100% correlation with the rabbit neutrali-

zation test, the correlation (94%) is high enough to make the test worthy of use in both epidemiologic and diagnostic studies. The studies presented in this paper done on a somewhat similar series of patients, both selected and unselected, seem to agree fairly well with the findings of Frenkel, since an 89% correlation was found between the rabbit test and the skin test (Table IV). However, in using the new slide neutralization test, as developed by Sabin and Feldman on the same group of patients, a higher correlation could be obtained with the rabbit test than with the skin test. This favors the slide neutralization test for use as a routine diagnostic procedure, rather than any of the other three tests. However, as Frenkel has stated, the disadvantage of having to maintain a live strain of Toxoplasma through constant passage in animals is a problem not to be overlooked.

We feel from our studies that the complement fixation test as performed in this study*

TABLE III

SIX PATIENTS WHO HAD REVERSAL OF POSITIVE TESTS FOR TOXOPLASMOSIS

Name	Age	Sex	Diagnosis	Rabbit	Slide	C.F.	Skin	Year Tested
1. C.J.	10	M	Hemophilia	+	...	...	...	1946
C.J.	11	M	Hemophilia	−	−	−	−	1948
2. B.K.	6 mos.	M	Subdural hematoma	+	...	...	...	1947
B.K.	12 mos.	M	Subdural hematoma	−	−	−	−	1948
3. L.R.	13 mos.	M	Encephalitis	+	...	1:4	...	1947
L.R.	14 mos.	M	Recovered	−	−	−	−	1948
4. V.K.	9	F	Rheumatoid	+	...	1:8	...	1946
V.K.	11	F	Recovered	−	−	−	−	1948
5. J.T.	8	M	Encephalitis	+	...	...	...	1946
J.T.	9	M	Recovered	−	...	...	...	1947
6. R.V.	1 mo.	F	Toxoplasmosis	+	...	...	...	1946
R.V.	2 yrs.	F	Toxoplasmosis	−	−	−	−	1948

+ Positive.
− Negative.
... Not done.

does not aid in determining whether or not an individual patient has been infected with Toxoplasma as this antibody may disappear rapidly from the blood stream in most individuals.[11] It may prove to be of value, however, as an indicator of the activity of acute disease or of a flare-up of a previous infection with Toxoplasma.

In epidemiologic or routine diagnostic studies, we feel that either the slide neutralization or the skin test may be adequate. If one of these tests is positive, then the rabbit and complement fixation tests may also be performed to further substantiate the diagnosis. The routine use of the slide test is more economical and the results will be obtained earlier. Since three of the sera on which the slide test was used showed a prozone type of reaction, it will probably be necessary in the future to run the slide test on both undiluted

* Further studies are in progress, evaluating other antigens for use in the complement fixation test.

and diluted serum. However, this should require no significant increase of time in performance of the test.

Studies from other parts of the United States have indicated that about 10% of the population at large have neutralizing antibodies against Toxoplasma in their sera.[12-14] From the group tested here, it appears that about 5 to 10% of the population of the State of Minnesota have antibodies against Toxoplasma. The number of patients tested is small,

TABLE IV

COMPARISON OF RESULTS OF RABBIT NEUTRALIZATION AND SLIDE NEUTRALIZATION TESTS

Rabbit Test		Slide Test	
		Positive	Negative
Positive	45 (100%)	45 (100%)	0
Negative	151 (100%)	7 (4.6%)	144 (95.4%)
Total	196	52	144

Rabbit Neutralization and Skin Tests

Rabbit Test		Skin Test	
		Positive	Negative
Positive	26 (100%)	23 (89%)	3 (11%)
Negative	117 (100%)	6 (5%)	111 (95%)
Total	143	29	114

Slide Neutralization and Skin Tests

Slide Test		Skin Test	
		Positive	Negative
Positive	33 (100%)	27 (81%)	6 (19%)
Negative	110 (100%)	2 (2%)	108 (98%)
Total	143	29	114

but a much larger study of the population is contemplated for the future now that the reliability of the slide and skin tests has been evaluated.

The loss of previously existing neutralizing antibodies against Toxoplasma has been observed to occur;[13] however, this phenomenon is not generally recognized. There is no question that sera previously tested from six of these patients showed definite neutralization of Toxoplasma. When these patients were retested at a later date, no evidence of antibodies or hypersensitivity to the toxoplasmin could be elicited. Three of these patients, R. V., V. K., and J. T. (Table III), seemed to improve clinically, and the reversal of the rabbit test from positive to negative occurred while they were receiving their trial therapy in the form of acetarsone.* The latter observation may have been purely coincidental,

* Further experimental therapeutic studies with this and other drugs are now in progress.

of course, since other patients known to possess antibodies against Toxoplasma have been observed to lose them over varying periods of time, without special therapy.

Summary

Results of a correlation study of the rabbit neutralization, complement fixation, skin and slide neutralization tests for toxoplasmosis are presented. The agreement between these is fairly striking, except those from the complement test.

Reversal of a positive test was found to occur in the sera of six patients, and, in three instances, the prozone phenomenon was revealed.

The new slide neutralization test of Sabin and Feldman appears to be the most accurate, the most economical and the quickest test available at present for the diagnosis of toxoplasmosis.

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Spanish Abstract

Ensayos Diagnósticos para Toxoplasmosis

Se presentan los resultados de un estudio de correlación de la neutralizacion de conejo fijación de complemento, ensayos de neutralización de lámina de vidrio y piel para la toxoplasmosis. El acuerdo entre estos ensayos es bastante notable excepto aquellos del ensayo de fijación de complemento. Este fué positivo solamente en un pequeño número de casos pareció tener su valor principal como un índice de actividad de la infección.

El contrario del ensayo positivo ocurrió en el suero de seis pacientes y en tres casos se reveló el fenómeno de prozona.

El nuevo ensaryo de neutralización de lámina de vidrio de Sabin y Feldman parece ser el más exacto, el más económico y el ensayo más ligero de obtener en estos momentos para la diagnosis de la toxoplasmosis.

En centros médicos donde no están preparados para llevar a cabo el ensayo de fijación de complemento o de conejo, en la lámina de vidrio, el ensayo de piel es talvez el más útil y práctico.

University of Minnesota Medical School

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY (BLAND-WHITE-GARLAND SYNDROME)

Report of Four Cases

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FOUR cases of anomalous origin of the left coronary artery from the pulmonary artery have been studied by the authors between the years 1938 and 1946. This anomaly was considered to be a pathologic curiosity until Bland, White and Garland[1] reported a case in 1933; they were the first to suggest the possibilities of a clinical diagnosis. In 1938, one of the authors (B. M. G.) of the study presented here made a clinical diagnosis of this anomaly. A study of these four cases, as well as of the cases published in the literature up to date, offers some suggestions as to the pathogenesis and possible treatment of this malformation.

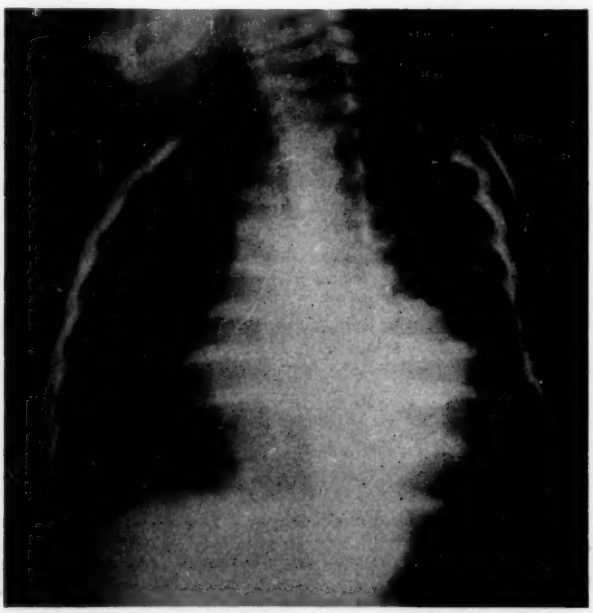

FIG. 1. (Case 1) Roentgenogram showing increase of transverse diameter of heart.

CASE REPORTS

Case 1. A baby, aged 5½ mos., was referred because of failure to gain wt., occasional loose stools, crying spells during and after feedings following which the baby became pale and perspired pro-

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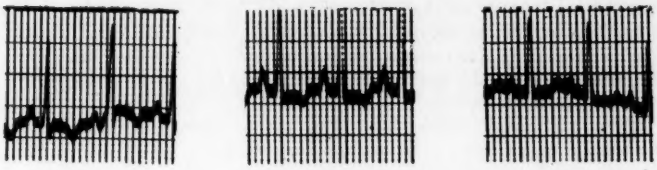
Lead 1
Lead 2
Lead 3
Lead No. 1. Between Right and Left Arms.
Lead No. 2. Between Right Arm and Left Leg.
Lead No. 3. Between Left Arm and Left Leg.

FIG. 2. (Case 2) Electrocardiogram.

fusely, and development of "colicky" attacks during the previous 2 mos. Past history was negative otherwise.

Physical examination revealed a poorly developed baby whose weight was 3.5 kg., and length, 53 cm. Heart was enlarged with the greatest diameter on the roentgenogram in the A-P view 8.5 cm., and of the chest, 12 cm. (Fig. 1). Pulse was regular, 120 to 130/min. There was no murmur or cyanosis.

Patient was hospitalized and tests for glycogenesis and glycogenolysis were performed. Repeated urine examinations for acetone were always negative. Two fasting blood sugar determinations were 119 and 100 mg./100 cc., and a blood sugar tolerance test started at 119 mg. went up to 160 and down again to 110 within 3 hrs.

Electrocardiogram showed normal axis deviation, tachycardia, ST_1 and ST_2 depressed, T_1 and T_2 inverted (Fig. 2). The cardiologist reported this to be a case of coronary thrombosis.

Repeated fluoroscopic and roentgenographic examination revealed that the hypertrophy involved the L. ventricle and the last roentgenogram showed an aneurysmal dilatation of the L. ventricle (Figs. 3 and 4).

The episodes of dyspnea, pallor and excessive perspiration continued and the infant died during 1 of the attacks at the age of 13 mos. An autopsy could not be obtained.

Case 2. (See Figs. 5 and 6.) This patient, aged 3 mos., had been delivered by cesarian section.

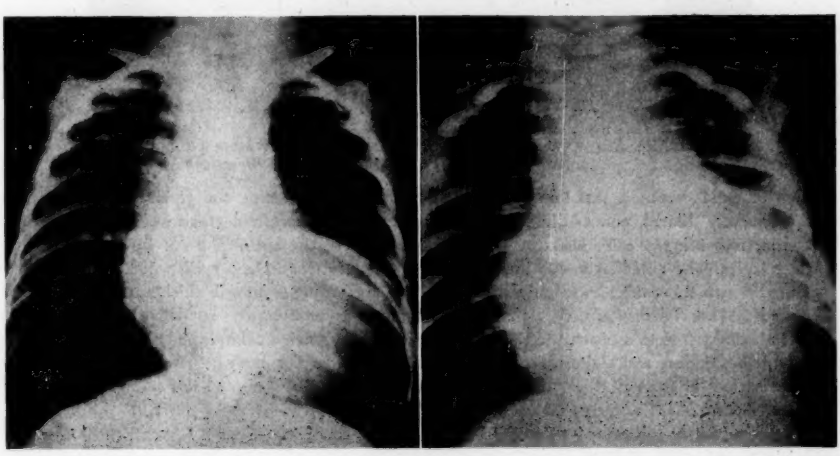

FIG. 3. (Case 1) Roentgenogram now showing what was probably aneurysmal dilatation of L. ventricle.

FIG. 4 (Case 2) Roentgenogram showing marked increase of transverse diameter of heart in P-A view.

Birth wt. was 4.1 kg. He had "colicky" pains which had developed during the previous week, especially during feedings. Mother stated that the respirations had become rapid, a slight cough had developed during the morning of her visit and temperature had always been normal.

Physical examination revealed a well developed baby, weighing 5.8 kg. Temperature was 37.4°C., pulse 130 to 140/min. and respirations 50/min. The marked dullness over the cardiac area extended to the 5th ICS to the anterior axillary line. There was no cyanosis, no cardiac murmur and no clubbing of the fingers or toes. Blood counts and urine were normal.

Because of the history and findings, a provisional clinical diagnosis was made of an anomalous left branch of the coronary artery arising from the pulmonary artery instead of the aorta. No ECG was made. Patient died the same day.

Postmortem Examination (Dr. Ernst Loeffler).—Pericardial sac contained 5 cc. of clear fluid. Heart weighed 180 gm., much enlarged, apex rounded, formed by the L. ventricle exclusively; longitudinal diameter measured 7.5 cm., the transverse 9 cm. Palpation revealed that the anterior apical

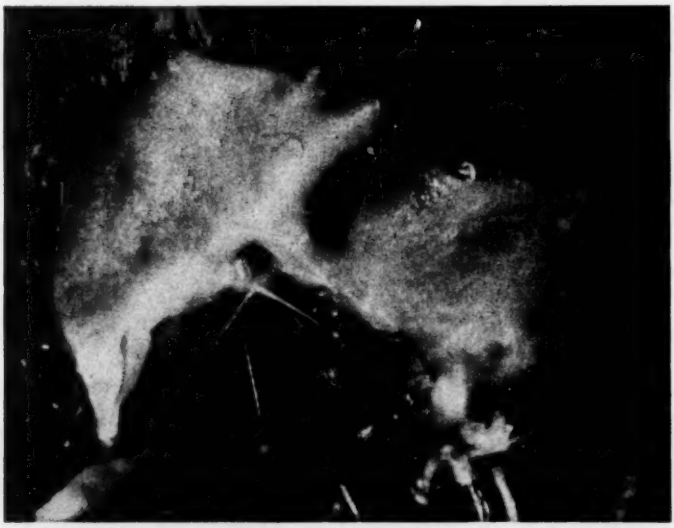

FIG. 5. (Case 2) Arrow points to origin of L. coronary artery from pulmonary artery.

portion of the L. ventricle was thin. Epicardium was smooth, glistening and greyish-red. L. ventricle was extensively dilated, endocardium diffusely thickened, glistening and greyish-white; myocardium was firm, measuring 9 mm. near the base and 1 mm. near the apex. The cut surface revealed 2 distinct layers. The outer layer was brownish-red, the inner layer light greyish-white. Mitral ostium measured 4 cm. R. ventricle was only slightly dilated, measuring 3 mm. in thickness. Aortic ostium measured 2.5 cm. There was only a right coronary artery present, which originated behind the right cusp. Pulmonary ostium measured 3 cm.; a coronary artery originated behind the left cusp and divided in a large descending and a short circumflex branch; the descending branch curved downward on the anterior surface of the heart near the septum in the usual place of a normal left coronary artery; the 2nd short branch supplied the upper portion of the L. ventricle.

Measurements were: MO 4 cm., AO 2.5 cm., PO 3 cm., Tr. 0.6 cm., L. ventricle 9 mm., R. ventricle 3 mm.

Lungs were congested and somewhat edematous. Spleen weighed 16 gm. and was congested. Liver weighed 190 gm. and was congested. Kidneys weighed 50 gm. and showed congestion.

Microscopic Examination.—Heart: Sections of L. ventricular wall revealed hypertrophy of muscle fibers with fibrosis in between. The fibrosis increased towards the apex where the muscle fibers were

almost completely replaced by dense hyalized fibers, between which only groups of vaculated muscle cells were found. Endocardium was diffusely thickened throughout. Generally the fibrotic changes were near the endocardial rather than the pericardial surface.

Lungs: Alveolar walls were thickened, alveolar capillaries dilated. Many alveoli contained heart failure cells, often accumulated in small groups. Some were filled with red blood cells and fibrin, some contained white blood cells; many were filled with pink-staining fluid. Diagnosis: chronic congestion; foci of bronchopneumonia; edema.

Anatomic Diagnosis: Left coronary artery originating from pulmonary artery; extreme dilatation and hypertrophy of L. ventricle of heart; fibrosis of myocardium of L. ventricle; diffuse thickening of endocardium; relative incompetence of mitral valve; congestion of lungs, liver, spleen and kidneys.

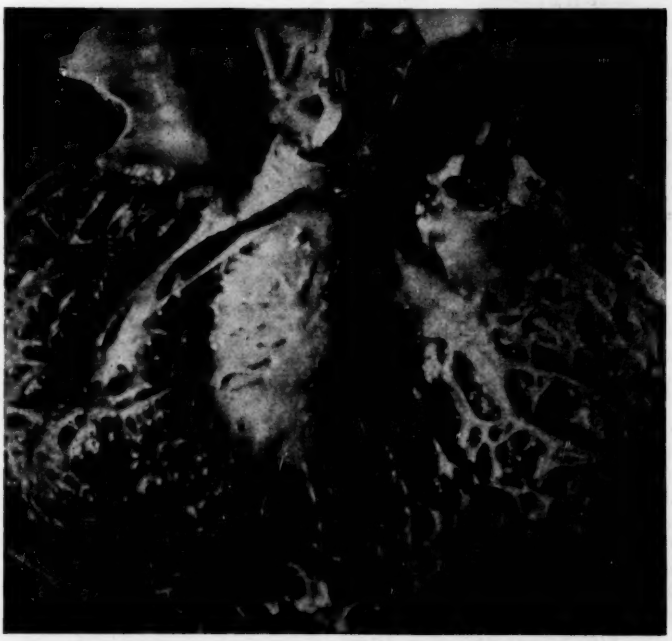

FIG. 6. (Case 2) Photograph of L. ventricle showing dilatation and hypertrophy of L. ventricle and thickening of endocardium.

Case 3. A female Negro infant, aged 7 mos., was admitted with a history of having had pneumonia 2 mos. previously, from which she recovered in 3 wks. Three days before admission, the baby developed a cough, again associated with fever.

Physical examination revealed no cyanosis and no murmurs. Dullness was noted over the L. lower lobe. A diagnosis of bronchopneumonia was made and the baby died on the same day before any studies could be made.

Postmortem Examination (Dr. Ernst Loeffler).—Abdominal cavity contained 10 cc. of amber clear fluid. Thymus was small, weighing about 5 gm. Pericardial sac contained 5 cc. of clear fluid.

Heart weighed 110 gm. Longitudinal diameter was 8 cm. It was much enlarged, 8:6.5:4.5 cm., compressing the L. lower lobe; the apex rounded, reaching the L. thoracic wall. Epicardium was smooth and glistening. Coronary arteries showed on the surface the usual distribution. The entire endocardium of the L. ventricle was thickened, glistening and greyish-white. Inner layers of the myocardium were lighter than the outer layer, which was dark brown; no fibrosis was seen grossly. Endocordium of the L. auricle was slightly thickened. R. ventricle was dilated and the wall was

hypertrophic. Left coronary artery originated from pulmonary artery, somewhat above left cusp. Right coronary originated in the usual place.

Measurements were: L. ventricle 9 mm., R. ventricle 7 mm., MO 5.5 cm., PO 3.2 cm., AO 3 cm., TO 6.5 cm.

Right lung weighed 110 gm. All lobes were edematous and the right lower lobe contained dense, prominent, greyish-red foci of bronchopneumonia. Left lung weighed 55 gm. Lower lobe was almost completely atelectatic due to compression by the heart; both lobes were edematous.

Microscopic Examination: Heart: Sections of the L. ventricle revealed the muscle fibers hypertrophic with areas of fibrosis in between, increasing in size and number towards the apex. Myocardium, however, was not completely replaced by fibrous tissue in the apex. Endocardium was diffusely and markedly thickened.

Anatomic Diagnosis: Left coronary artery originating from pulmonary artery; eccentric hypertrophy of both ventricles of heart (110 gm.); diffuse thickening of endocardium of L. ventricle and auricle; bronchopneumonia of R. lower lobe; partial atelectasis of L. lower lobe; edema of lungs; congestion of liver, spleen and kidneys.

Case 4. A Negro female infant, 3 mos. of age, was admitted with the chief complaint of difficulty in breathing noted soon after birth which had become much more pronounced during the past wk. There was no fever, cough or cyanosis at any time. Birth wt. was 3.6 kg. On examination, the baby weighed 4.9 kg.; ht. was 52 cm. Temperature 37.4°C. (R), pulse 120/mm. and respirations 90/min. There was no cyanosis or clubbing of fingers or toes. There was dullness in the L. chest anteriorly extending to the anterior axillary line in the 5th ICS. There were no murmurs.

Roentgenogram of chest showed a diffuse enlargement of the heart and ECG showed a tachycardia, low amplitude QRS complex, inversion of the T waves in all leads.

Postmortem Examination.—Right pleural cavity contained about 3 cc. of clear straw colored fluid. L. cavity about 4 cc. of the same fluid. Pericardial cavity contained about 4 cc. of clear, straw colored fluid. Pericardial surface was smooth and shiny.

Heart measured 6 cm. from apex to base, 5 cm. at its widest portion and 3 cm. in thickness. It appeared to be enlarged. Apex was formed mainly by the L. ventricle. Epicardium was smooth and glistening. There was little fat present. Myocardium was firm. All cardiac chambers were dilated. Myocardium was reddish-brown in color. Right auricle was dilated and measured 3x2.5 cm. R. ventricle was dilated and measured 5x3 cm. The wall measured 3 mm. in thickness. Valves were thin and delicate. Trabeculae were moderately prominent. Endocardium was smooth. Left auricle was dilated and measured 3x3 cm. L. ventricle was markedly dilated and measured 5 cm. from apex to base and 7 cm. transversely. Wall was 8 mm. thick. The trabeculae cornae were flattened with marked cupping present at the apex. Papillary muscles were not hypertrophied and were 4 mm. in width. At the apex and the chordae tendinae marked arteriosclerotic changes were present and appeared yellow-grey in color. Chordae tendinae showed a slight tendency to fusion at the distal aspect. Endocardium showed a considerable degree of thickening. On section the myocardium was a deep reddish tan.

Mitral valve measured 3 cm., tricuspid valve 5 cm., aortic valve 2 cm. and pulmonary valve 2.5 cm. Interventricular septum and interauricular septum were intact. The ductus arteriosus was patent and admitted a fine probe. Right coronary artery arose from just above the R. cusp of the aortic artery. Left coronary artery arose from the L. pulmonic cusp and about 1 cm. from its origin divided into the L. circumflex artery and the L. descending coronary artery.

Microscopic Examination.—Sections of the L. ventricle revealed hypertrophy of muscle fibers with foci of fibrosis in between. This replacement fibrosis increased toward the apex, where a considerable amount of muscle fibers disappeared; there was, however, no complete fibrosis of the entire wall. Sections through the papillary muscle showed multiple areas of calcification, especially near the apex. Entire endocardium was diffusely thickened. Sections of the R. ventricle showed no fibrosis.

Anatomic Diagnosis: Left coronary artery originating from pulmonary artery; extreme dilatation and hypertrophy of L. ventricle of heart; fibrosis of myocardium of L. ventricle; diffuse thickening of endocardium; bronchopneumonia of R. upper and L. lower lobes of lung.

Comment

Twenty-two cases[1-22] of an anomalous origin of the left coronary artery from the pulmonary artery have now been reported in the literature (Table I). The additional four

cases in this study make a total of 26 cases. Five of these cases lived to adulthood. None of these five adults had symptoms referable to their anomaly and in all five cases autopsy revealed definite collateral circulation between the two coronary arteries. Of the remaining 21 cases, all except two died between three and six months of age. Two lived to 13 months.

Bland, White and Garland[1] found eight other cases reported in the literature, six of which occurred in infants under one year of age. None of the cases had had ECG and the clinical condition was not suspected. Their case was the only one in which an electrocardiographic study was made and they suggested that "in future cases of uncomplicated cardiac hypertrophy in infancy, the finding of a similar electrocardiogram in the absence

TABLE I

REPORTED CASES UP TO DATE

Authors	Yr. Reported	Age Mos.	Age Yrs.
Abrikosoff	1911	5	
Heitzmann	1917	3½	
Kiyokawa	1923	4	
Carrington and Krumbhaar	1924	10	
Scholte	1930	2½	
Stevenson		3	
Abbott			64
Bland, White and Garland	1933	3	
Kockel	1934		38
Sanes and Kenny	1934	3	
Bartsch and Smekal	1934	3	
Linck	1936	8	
Chown and Schwalm	1936	5	
Rübberdt	1937		27
Barnard	1938	4½	
Dietrich	1939		53
Soloff	1942	4½	
Ruddock and Stehly	1943		30
Proescher and Baumann	1944	13	
Eidlow and Mackenzie	1946	4	
Lyon, Johansmann and Dodd	1946	6	
Lyon, Johansmann and Dodd	1946	3	
Gasul	1938	13	
Gasul and Loeffler	1946	3	
Gasul and Loeffler	1946	7	
Gasul and Loeffler	1948	3	

of abnormal axis deviation, or toxemia, may indicate an inadequate and anomalous coronary supply to the heart."

The infants reported were apparently healthy at birth and developed normally until two or three months of age when they began to have "colicky" pains, usually occurring during or soon after feedings, associated with a rapid pulse, rapid respirations, pallor and profuse perspirations. They all showed an enlarged heart and, in those cases where an electrocardiogram had been taken, inversion of the T waves in the leads was noted, but there was no axis deviation. Low amplitude of the QRS complexes was usually noted.

Following the publication of Bland, White and Garland's paper, Soloff[17] reported a

case in an infant 4½ mos. of age, on whom no clinical diagnosis had been made, but whose autopsy revealed the same characteristic pathologic picture.

Ruddock and Stehly[18] reported a case of an adult aged 30 yrs. who died suddenly. Autopsy revealed the origin of the left coronary artery from the pulmonary artery and the left coronary communicated with the terminal branch of the right circumflex artery over the basal portion of the central surface of the left ventricle.

Proescher and Baumann[19] reported a case of an infant, aged 13 mos., in whom the diagnosis was made at autopsy. Eidlow and Mackenzie[20] reported a case of an anomalous origin of the left coronary artery from the pulmonary artery diagnosed clinically and confirmed by autopsy. The infant died at the age of 4 mos. Lyon, Johansmann and Dodd[21] reported two additional cases, one infant dying at the age of 6 mos. and the other at the age of 3 mos.

The fact that the four cases presented here were seen in a comparatively short time points to the possibility that the condition is not as unusual as a review of the literature would lead one to believe. Some of these cases have probably been called idiopathic cardiac hypertrophy; others might have been labeled as "thymic deaths." It is felt that as a result of familiarity with this entity more cases will be recognized.

The entity has well defined pathologic features. All the cases show hypertrophy and dilatation of the left ventricle and myocardial degeneration which in some cases goes on to complete fibrous tissue replacement in the regions supplied by the left coronary artery. The explanations that have been offered for the marked enlargement of the left ventricle and for the degenerative changes in the myocardium are two-fold: first is the fact that the left coronary brings nonoxygenated (venous) blood to the left ventricle and, second, the low pressure existing in the pulmonary artery as compared to the aorta. These viewpoints are obviously correct. However, it would seem that the myocardial damage is too severe and progressive to be explained by venous blood and low pressure only. The attacks simulating angina pectoris suggest an additional factor. The fact that no myocardial damage whatsoever is found if the right coronary originates from the pulmonary artery and the fact that extensive anastomosis can prevent myocardial damage point to an additional factor. Low pressure and venous blood will lead to impairment of the functional capacity of the left ventricle. The dilated heart performs more mechanical work and the oxygen consumption goes up. Dilatation is the basis on which hypertrophy arises, even though the absolute work of the heart is not augmented. There is a relative increase in the sense that the actual work performed approaches more closely the maximum of the heart's capability. The dilatation and subsequent hypertrophy will lead to a temporary and permanent compression of parts of the left coronary artery which has a lower pressure than a normal left coronary artery. As in any case of dilatation, the parts near the ventricular apex are dilated first and most. It is the compression of the coronary artery starting near the apex and in time progressing towards the base which is responsible for the extensive fibrosis of the myocardium. The more replacement of myocardium by granulation tissue and later fibrous tissue, the more pronounced will be the bulging of the left ventricle and the more extensive and complete will be the occlusion of the left coronary artery which again, in a vicious circle, will lead to additional myocardial damage. This would seem to be the explanation for severe fibrosis simulating the picture of coronary occlusion in adults.

Another point that so far has not as yet been noted or discussed is this: All the reported cases apparently were well for a while and then began having symptoms during the second

or third months of life. Not one of them died before 2½ to 3 mos. of age. The following speculation may be offered as an explanation:

During fetal life, the lungs do not function for all practical purposes and the pressure in the lesser circulation is higher than in the systemic circulation so that blood is directed through the ductus arteriosus into the aorta. There is also little or no difference in the oxygen saturation of the blood from the pulmonary artery and that of the aorta, so that at birth the babies are born with a normal heart.

The ductus arteriosus begins to close soon after birth and in the average case it is closed by the end of the second or third month. But since the pressure existing in the lesser circulation is about equal to that of the greater circulation during the first two or three months of the baby's life, there is usually no flow of blood in either direction, and even though the ductus arteriosus may be patent anatomically, functionally it closes soon after birth, because of the equilibrium in the existing pressure relationship between the two circulations.

It is well known, for example, that the electrocardiogram shows a slight right axis shift during the first two or three months of the infant's life. So long as the pressure in the pulmonary circulation is as high as it is in the greater circulation, so long will the blood flow through the left coronary artery into the left ventricle under at least as much pressure as the blood that flows through the right coronary artery to the right ventricle. The nutrition of the myocardium of the left ventricle will not be as good as that of the right ventricle because it will receive nonoxygenated blood. However, the important point to remember is that even venous blood contains 75% oxygen. Anyone who sees cyanotic infants and children with congenital malformations of the heart knows that they may live many years with an arterial oxygen saturation well below 75% and yet none of them show either the pathologic picture or the electrocardiographic findings that are present in this malformation. It is doubtful if it even makes much difference whether or not some oxygenated blood will enter the left coronary artery from the aorta through the patent ductus. The important point is the pressure relationship existing between the greater and lesser circulation.

But after the second or third month of life, the ductus usually closes, and, what is more important for these cases, the pressure in the aorta becomes definitely higher than in the pulmonary artery, and it is then that the symptoms and the clinical findings of this malformation become evident. It is probably not so much the difference in the oxygen saturation as the low pressure in the left coronary artery that gives rise to the clinical and pathologic picture of this malformation, and since this low pressure does not really appear until about the third month, infants do not manifest any symptoms until then.

Suggested Treatment

Since this is an apparently uniformly fatal disease, it would seem reasonable to attempt to raise the pressure in the pulmonary artery and at the same time try to supply oxygenated blood to the left branch of the coronary artery by anastomosing the pulmonary artery to the aorta. It is suggested that either a Potts-Smith operation to connect the left or right pulmonary artery to the descending aorta be performed, or, even better, if this is technically possible, attempt to anastomose the main pulmonary artery to the ascending aorta. This would then direct oxygenated blood closer to the origin of the coronary artery than if a Potts-Smith operation were performed.

The difficulties connected with the performance of this type of an operation on young

infants are apparent. A review of the reported cases will show that in some instances a clinical diagnosis had been made several weeks or months before death, however, and it is possible that surgical intervention of the type suggested might have been successful on these patients.

Conclusions

The anomalous origin of the left coronary artery from the pulmonary artery is a definite pathologic and clinical entity. A review of the literature reveals 22 reported cases. Four additional cases are presented. Additional considerations explaining observations in this syndrome and a suggestion for the possible treatment of this malformation are presented.

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SPANISH ABSTRACT

Origen Anómalo de la Arteria Coronaria Izquierda de la Arteria Pulmonar (Síndrome Bland-White-Garland)

Se informa acerca de cuatro casos y una revista de literatura de hipertrofia cardíaca en infantes debida a un origen anómalo de la arteria coronaria izquierda de la arteria pulmonar. La diagnosis está basada en el caso de un nacimiento aparentemente normal y de desarrollo normal hasta la edad de 2 a 3 meses, cuando venían dolores cólicos, generalmente durante o luego después de comer, y los exámenes revelaron un corazón ensanchado, pero no cianosis ni murmullos. El ensanchamiento es debido a la dilatación del ventrículo izquierdo, lo que se puede ver mejor por medio de un examen fluoroscópico en la vista oblicua anterior izquierda. En esta vista el conducto de aflujo del ventrículo izquierda se ve definitivamente ensanchado, y no importa cuanta giración se le dé al paciente, es difícil que el ventrículo izquierdo aclare la espina. En algunos casos, una dilatación aneurismal del ventrículo izquierdo tiene lugar, y el EEG muestra complejos QRS de baja amplitud e inversión de las ondas T, pero no una desviación del axis. Este síndrome se puede diferenciar de todas las otras condiciones que causan ensanchamiento cardíaco en la infancia por los criterios presentados.

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ELECTROPHORETIC STUDIES OF PLASMA PROTEINS IN NORMAL CHILDREN

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ELECTROPHORETIC analysis has been widely used in recent years as a method of study of the various components of the plasma proteins. The method has proved to be a valuable tool in the study of a great many diseases in which marked deviations from the normal electrophoretic pattern of plasma occur. For evaluation of the changes occurring in disease, the electrophoretic pattern of plasma proteins in healthy adult men has been used as the standard of comparison. Studies on normal men reported from different laboratories show good agreement for percentage distribution of protein fractions.

Although Longsworth and co-workers[1] have shown that the newborn infant has an unusually high γ-globulin concentration, few studies in children which would determine changes in electrophoretic pattern with increasing age have been reported. Recently as a part of a study of immunologic and biochemical factors in the etiology of rheumatic fever, Lubschez[2] published electrophoretic analyses of plasma proteins in 30 healthy children between the ages of 2 and 11 years. Of primary interest to the author was the effect of antecedent infection on the normal pattern. Lubschez noted that the relative concentration of the various protein fractions was similar to normal adult values, although the percentage of albumin tended to be somewhat higher and the percentage of γ-globulin somewhat lower in the younger children.

The present study was undertaken to establish the normal electrophoretic patterns for use in interpreting changes from normal occurring in children with nephrosis and rheumatic fever being studied in this laboratory;[3, 4] and to determine any fundamental changes in distribution of plasma proteins related to age and immunologic maturity.

EXPERIMENTAL

The subjects for this study were 54 healthy children ranging in age from birth to 17 yrs., including 16 girls and 38 boys. The data were collected during 1947 and 1948. The infants were housed in the metabolism ward of the hospital where they were subjects for studies of mineral and protein nutrition in the normal infant. Some of the older children were subjects for similar studies; others were from faculty and town homes of a university community. All the children had been free of any cold or other minor infection for at least 1 mo., often considerably longer. The "normality" of the subjects was checked by determination of erythrocyte sedimentation rate, hemoglobin, red and occasionally white blood cell counts. If any of these values varied markedly from the accepted normal levels, the electrophoretic data were excluded from this study.

Blood samples were taken when the subjects were in a fasting state if possible and always at least 3 hrs. after meals. Potassium oxalate was used as the anticoagulant. Plasma samples were refrigerated for an interval of 1 to 4 days between the time they were withdrawn and analysis obtained. They were diluted with buffer to a protein concentration of 1.5 to 2.5% and dialyzed in a Visking casing at 2° to 6°C. for 3 days with daily change of buffer. Electrophoresis was carried out in the Tiselius apparatus at pH 8.6 in sodium diethyl barbiturate buffer according to the Longsworth[6] procedure. Schlieren diagrams, photographically enlarged, were traced with a planimeter, according to the method of Pedersen,[6] to obtain the percentage of the total area attributed to each

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protein fraction. Total protein and plasma fractions also were determined according to the Howe method with 22% sodium sulfate, micro-Kjeldahl digestion and Nesslerization.

Some of the plasma samples from the infants showed a distinct hyperlipemia which interfered with photography of the Schlieren diagrams. Clarification of the samples by high-speed centrifugation, together with photographic compensation by the use of light filters and increased illumination, usually was successful in eliminating this interference.

Mobility measurements were made from the boundary anomaly of the pattern. These measurements were made for each pattern analyzed and the values obtained agreed with published values for mobilities of individual protein fractions.

Results and Discussion

The percentage composition of the plasma proteins determined by electrophoresis for the 54 children is given in Table I. Also included are the mean values and standard deviations for four age groups. These groups are infants, 6 to 46 weeks of age; preschool, 1 to 4 years; midchildhood, 5 to 11 years; and adolescents, 13 to 17 years. The values for any one fraction show considerable individual variation, as is indicated by the fairly large standard deviations. Nevertheless, both the mean values for the different age groups and the standard deviations agree reasonably well with values for normal adults reported by Dole et al.,[7] Deutsch and Goodloe,[8] and Dryer et al.[9] using similar technics.

With increasing age, only minor changes occurred in most fractions. Mean values for the percentage of albumin for three age groups were remarkably consistent, but children 5 to 11 years of age showed a significantly lower albumin percentage. The value of Fisher's "t" for the difference between the group 1 to 4 years and the group 5 to 11 years was 3.07, and for the group 5 to 11 years and the group 13 to 17 years was 3.77, both values being highly significant. Lubschez[2] also noted a somewhat higher albumin percentage in the younger children. Actually, her figures for albumin changes with age are similar to ours; the mean value for 9 children 2 to 4 years of age was 62.2% as compared to our value of 60.6% for 10 children 1 to 4 years, and the mean for 21 children 5 to 11 years was 57.3% compared to our value of 56.6% for 17 children of the same age. For the adolescent children, the albumin percentage was increased to 60.6. This value is almost identical with the percentages for the two youngest age groups and similar to the values reported for normal adults, which ranged from 59.6 to 61.5%.

A small but persistent decrease in the percentage of α_1-globulin was noted. The changes in α_2-globulin with increasing age were more striking. The value of 12.9% for infants is significantly higher than the mean value of 8.4% for three studies of normal adults. In the 1 to 4 year group, the α_2-globulin percentage had decreased to 10.7%, and in the 5 to 11 year group to 9.8%. No further change occurred in the adolescent children. The decrease from 12.9% to 9.8% is statistically significant ("t" = 5.07). At present there is no explanation for these variations in α_2-globulin percentage with age.

The most striking changes with age were observed in the γ-globulin fraction. Studies of cord blood from two newborn babies (Table I) confirmed the findings of Longsworth[1] that the γ-globulin percentage in newborn infants often is above the normal adult level. Although we were not able to follow changes in electrophoretic pattern with age in these infants as we had hoped to do, we do have successive patterns for two normal infants included in the group of 11 normal infants. Infant KM showed a decrease in γ-globulin from 3.5% at 8 weeks to 1.8% at 17 weeks; and infant MK showed a decrease from 5.6% at 12 weeks to 2.9% at 22 weeks. Apparently the passive immunity received by the infant from its mother is gradually lost during early infancy.

TABLE I

ELECTROPHORETIC ANALYSES OF PLASMA PROTEINS IN NORMAL CHILDREN

Subject	Sex and Age	Total Protein gm./100 ml.	Percentage Composition						Alb./Glob.
			Alb.	Globulins					
				α_1	α_2	β	θ	γ	
S	M Newborn	5.4	62.6	6.3	7.9	9.8	3.5	9.9	1.67
H	F Newborn	5.6	55.8	8.5	7.5	9.1	3.0	16.1	1.26
	Wks.								
R.H.	M 6	5.6	59.9	8.6	9.5	10.2	5.6	5.6	1.49
K.M. (1)	F 8	5.9	63.3	5.8	12.2	11.1	4.1	3.5	1.72
M.K. (1)	F 12	6.0	58.8	8.2	14.3	10.8	2.3	5.6	1.43
K.M. (2)	F 17	6.3	60.1	8.5	15.4	11.6	2.6	1.8	1.51
H.S.	M 19	6.8	55.0	8.1	12.7	11.9	7.7	4.6	1.22
M.K. (2)	F 22	6.5	61.4	5.9	13.0	12.6	4.2	2.9	1.59
C.M.	F 22	5.3	58.5	3.7	13.4	15.8	5.5	3.1	1.41
R.T.	M 23	7.7	65.6	4.0	12.2	11.9	3.3	3.0	1.91
J.H.	F 25	5.6	57.9	6.3	12.3	11.1	5.6	6.7*	1.38
D.F.	M 27	6.5	66.2	4.6	13.1	10.8	2.1	3.2	1.96
J.D.	M 31	6.6	64.5	9.5	13.0	8.5	2.4	2.1	1.82
S.H.	F 34	5.8	55.3	4.6	16.2	10.6	6.3	7.0*	1.24
N.S.	F 46	6.8	65.6	7.2	13.2	11.2	1.6	1.2	1.91
Mean		6.4	61.7	6.7	12.9	11.5	3.8	3.3	1.63*
S D		.62	3.76	2.03	1.47	1.75	1.86	1.32	.27
	Age in yrs. and mos.								
M.B.	M 1-6	7.7	64.8	7.3	7.3	15.0	2.3	3.3	1.84
M.R.	M 1-9	6.0	62.7	6.9	7.9	14.0	2.2	6.3	1.68
K.C.	F 2-4	6.5	61.1	7.5	12.5	11.4	2.5	5.0	1.57
E.C.	M 3-5	6.3	58.9	6.5	10.6	13.0	3.1	7.9	1.43
M.N.	M 3-5	7.7	55.0	7.7	17.9	9.7	4.7	5.0	1.22
G.D.	F 4-2	7.4	55.5	7.9	8.2	16.1	4.4	7.9	1.25
P.F.	F 4-4	6.9	63.5	3.6	9.8	13.2	3.0	6.9	1.74
R.Mc.	M 4	7.7	61.3	6.8	11.2	8.5	5.4	6.8	1.58
G.N.	M 4	8.3	64.0	6.1	9.9	5.6	4.1	10.3	1.78
B.M.	M 4	7.5	59.6	3.0	11.5	6.9	6.9	12.1	1.48
Mean		7.2	60.6	6.3	10.7	11.3	3.9	7.2	1.56
S D		.74	3.29	1.70	3.28	3.70	1.53	2.58	.26
B.Br.	M 5-3	6.7	59.8	7.1	7.3	16.8	3.5	5.4	1.49
F.M.	M 5	8.7	60.3	6.1	10.1	5.5	4.7	13.3	1.52
B.F.	F 6-3	7.3	56.7	5.5	8.1	17.0	3.8	8.9	1.31
S.N.	M 6	7.2	61.6	5.5	8.4	6.9	5.3	12.3	1.60
D.M.	M 6-11	8.0	53.0	8.2	9.0	15.1	6.0	8.7	1.13
B.B.	M 7	6.8	61.7	6.4	10.3	7.3	5.2	9.1	1.61
F.H.	M 7	7.6	55.2	5.2	10.7	11.1	5.9	11.9	1.23
E.E.	M 7-4	7.4	52.9	9.5	9.5	11.9	8.6	7.6	1.12
J.F.	M 7-7	6.9	63.5	3.6	9.8	13.2	3.0	6.9	1.74
D.C.	M 8	7.1	54.1	5.6	10.6	13.4	6.6	9.7	1.18
R.C.	M 8	8.0	54.8	3.9	9.8	14.1	6.2	11.2	1.21
B.W.	M 9	7.2	55.4	9.2	9.9	7.6	7.6	10.3	1.24
L.T.	M 9	8.6	51.8	4.7	9.7	16.4	6.0	11.4	1.07
L.H.	M 10	8.1	54.8	4.2	8.1	12.9	5.4	14.6	1.21
E.B.	M 10	8.1	52.8	5.7	12.3	14.3	7.6	7.3	1.12
C.D.	M 10	8.2	55.3	5.4	11.7	12.6	6.7	7.8	1.24
C.S.	F 10-11	6.7	58.1	9.5	11.3	8.2	4.3	8.7	1.38
Mean		7.6	56.6	6.2	9.8	12.0	5.7	9.7	1.32
S D		.68	3.40	1.88	1.33	3.67	1.52	2.46	.23
N.K.	M 13-0	7.1	61.2	5.1	12.2	9.5	4.8	7.2	1.58
S.H.	M 13-1	7.8	60.3	4.3	10.3	12.8	4.7	7.7	1.52
E.T. (1)	F 13-6	7.6	57.1	4.6	9.6	12.0	5.0	11.7	1.33
D.K.	M 13-7	7.3	61.9	4.3	10.2	10.2	5.5	7.9	1.62
E.C.	F 14	6.7	57.8	3.6	9.1	10.2	4.4	14.9	1.37
H.B.	M 14	6.6	61.4	10.4	8.9	11.2	3.5	4.6	1.59
R.B.	M 14-3	7.9	63.3	3.9	11.0	9.6	5.2	7.0	1.72
E.T. (2)	F 15-2	7.7	61.6	4.2	9.0	9.7	4.8	10.7	1.60
P.M.	M 15-6	7.0	58.0	6.9	12.1	11.5	4.6	6.9	1.38
C.M.	M 15-8	6.7	59.8	4.6	7.8	13.9	5.4	8.5	1.49
D.V.	M 15-11	6.8	61.2	5.7	8.2	12.6	4.9	7.4	1.58
T.H.	M 17-2	7.7	60.5	3.6	10.7	10.7	7.1	7.4	1.53
A.H.	F 17	7.2	59.8	3.7	6.1	12.1	6.5	11.7	1.49
C.S.	M 17	7.5	65.0	5.8	10.1	6.7	3.8	8.7	1.85
Mean		7.2	60.6	5.0	9.7	10.9	5.0	8.7	1.54
S D		.45	2.13	1.80	1.66	1.51	.93	2.64	.14

* Data for subjects J.H. and S.H. not included in mean figures. See discussion.

Lubschez[2] found that illness or infection within a period of one to four months prior to the determination of the electrophoretic pattern produced an elevation in γ-globulin percentage in a large proportion of subjects. Although we were unable to control our subjects as closely as Lubschez did, our children were free of known infection for a minimum of only one month and our mean values agree closely with hers. In fact, the range of values for our subjects is somewhat narrower and standard deviations smaller. Partial explanation of the more consistent results may lie in the fact that most of the children in our study came from the rather protected environment of a fairly high social-economic group in a partly rural, small town area. Confirmation of Lubschez' findings regarding the effect of antecedent infection was obtained with the two infants, JH and SH in Table I, whose values are not included in the mean. Although no apparent illness

TABLE II

ELECTROPHORETIC ANALYSES OF PLASMA PROTEINS IN NORMAL PERSONS FROM BIRTH TO MATURITY

Age	Source of of Data	No. of Sub-jects	Percentage Composition					
			Alb.	Globulins				
				α_1	α_2	β	θ	γ
Newborn	Longsworth[1]	11	61.9	4.7	8.0	9.7	5.3	15.7
Newborn	Authors	2	59.2	7.4	7.7	9.5	3.2	13.0
6–46 wks.	Authors	11	61.7	6.7	12.9	11.5	3.8	3.3
2– 4 yrs.	Lubschez[2]	9	62.2	4.5	9.1	14.3	4.0	7.2
1– 4 yrs.	Authors	10	60.6	6.3	10.7	11.3	3.9	7.2
5–11 yrs.	Lubschez[2]	21	57.3	5.1	9.7	11.9	5.7	10.4
5–11 yrs.	Authors	17	56.6	6.2	9.8	12.0	5.7	9.7
13–17 yrs.	Authors	14	60.6	5.0	9.7	10.9	5.0	8.7
Adult men	Dole[7]	15	60.3	4.6	7.2	12.1	5.1	11.0
	Deutsch[8]	3	59.6	6.7	8.8	11.0	4.8	9.1
	Dryer[9]	16	61.5	4.7	9.4	10.8	5.2	8.4
	Mean Adult	34	60.8	4.8	8.4	11.4	5.1	9.6

had been observed and the values for sedimentation rate, red blood cell count and hemoglobin were normal, the temperature record was checked in an attempt to explain the obviously high values for γ-globulin. Each of the children was found to have had an elevated temperature reading of 37.8° to 38.4°C. 7 to 10 days prior to the withdrawal of blood for analysis. Apparently the minor infection was sufficient to bring about a marked increase in the γ-globulin fraction of plasma protein.

A steady increase in the γ-globulin component occurred from infancy through mid-childhood. No further increase, in fact, a slight decrease, occurred during adolescence. The increase from a mean value of 3.3% for infants to 7.2% for the 1 to 4 year group was statistically significant ("t" = 3.44). An additional increase from 7.2% to 9.7%

(significant only at the 5% level of confidence) occurred in the children 5 to 11 years old. A similar increase in the percentage of γ-globulin in this latter age group was reported by Lubschez.[2] Probably the gradual increase in the concentration of γ-globulin reflects the increased production of antibodies and the development of active immunity during childhood.

In Table II are summarized the data from this study and from the literature for percentage distribution of plasma protein fractions determined by electrophoretic analysis for different age groups from the newborn to adulthood. All studies included in Table II were made using the Longsworth technic and therefore are comparable. Changes with

TABLE III

CONCENTRATION OF PLASMA PROTEINS IN NORMAL CHILDREN*

Age	No.	Alb.	Globulin					A/G
			α_1	α_2	β	θ	γ	
		gm./100 ml.						
6–46 wks.	11	3.92	0.43	0.82	0.74	0.24	0.21	1.56
1–4 yrs.	10	4.37	0.46	0.77	0.80	0.28	0.52	1.56
5–11 yrs.	17	4.23	0.47	0.75	0.91	0.45	0.76	1.32
13–17 yrs.	14	4.40	0.36	0.70	0.79	0.36	0.63	1.54

* Estimated from chemical analysis of total protein and percentage composition by electrophoretic analysis.

age are most prominent for γ-globulin. The decrease from values of 13 to 15.7% for newborn infants to a mean value of 3.3% for infants under one year indicates a fairly rapid loss of the passive natural immunity received from the mother. Gradually, as a result of artificial immunizations and infections, antibodies are accumulated constituting acquired active immunity. The child apparently reaches the adult level of immunity in midchildhood and, unless exposed to infection, which caused a temporary increase in γ-globulin,[2] thereafter the γ-globulin percentage in health remains relatively constant.

Apparently a reciprocal relationship obtains between α_2-globulin and γ-globulin. The percentage of α_2-globulin is low in the newborn infant, rises above the normal adult level in infancy and gradually decreases toward the adult level with age; whereas, the γ-globulin percentage is high in the newborn, decreases rapidly in early infancy to low levels, and then gradually increases to the normal adult level in midchildhood. Present knowledge of the function of α_2-globulin is insufficient to clarify this reciprocal relationship. It is recognized that during the acute febrile stage of an infection, a rise in α-globulins occurs, followed later by the rise in γ-globulins.[10]

For greater usefulness in interpreting clinical data there are recorded in Table III the mean values for plasma protein fractions calculated in gm./100 ml. from the figures for total protein and percentage composition. These data show that the absolute concentration of γ-globulin also increases with age, reaching the highest level at 5 to 11 years. Confirming the findings for percentage composition, the increase from a value of 0.21 gm./100 ml. in infancy to 0.52 gm. at 1 to 4 years was statistically significant ("t" = 4.37), and the additional increase to 0.76 gm. for 5 to 11 years was significant

only at the 2% level of confidence. The concentration of γ-globulin during adolescence was slightly lower than in midchildhood but the difference was not significant. These data prove, however, that the increase in γ-globulin with age is not only relative but real. Since these figures are in gm./100 ml. and the blood volume in a child also increases with age, a substantial increase in the reservoir of antibodies for immunity is represented by these changes in γ-globulin.

The mean figures for actual albumin concentration listed in Table III also are interesting. In contrast to the figures for percentage of albumin, the mean concentration of albumin in gm./100 ml. for children 5 to 11 years old was only slightly less than for younger or older children. The marked decrease in percentage of albumin in midchildhood appears to be an artifact. Percentage values for fibrinogen and γ-globulin were higher in the 5 to 11 year group than in either younger or older children, the increases in these fractions accounting for the proportionate decrease in albumin percentage. Since the mean value for gm. of total protein is higher for children 5 to 11 years old, the increase in actual concentration of γ-globulin, fibrinogen, and other globulin fractions takes place without any significant decrease in absolute concentration of albumin.

Summary

Electrophoretic studies of plasma proteins have been made for 54 healthy children ranging in age from birth to 17 years. Mean values for most plasma protein fractions agreed well with previously published results for normal adults and children, but changes in the relative concentration of some of the components with age were noted.

Although the percentage of albumin decreased from infancy to midchildhood and appeared to be lowest in children 5 to 11 years old, figures for absolute concentration of albumin in gm./100 ml. showed no significant decrease in albumin for this age group.

The percentage and the absolute concentration of α_2-globulin were highest in infancy and decreased gradually with increasing age.

Both the percentage and the absolute concentration of γ-globulin decreased from unusually high values in the newborn infant to unusually low values in infancy, then gradually increased with age to reach the normal adult level in midchildhood, 5 to 11 years of age. These changes are believed to be related to the loss of passive immunity received by the infant from its mother and the accumulation of antibodies and the development of active immunity in the child.

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SPANISH ABSTRACT

Estudios Electroforeticos de Proteinas de Plasma en Niños Normales

Se han hecho estudios electroforeticos de las proteinas de plasma para 54 niños sanos de edas variando desde el nacimiento hasta 17 años. Todos los niños estaban libres de infecciones conocidas por lo menos un mes, a menudo por más tiempo. La electroforesia se llevó a cabo en el aparato Tiseluis a pH 8.6 en amortiguador barbirúrico de dietilo de sodio según el procedimiento de Longsworth. Los valores por composición de porcentaje de las seis fracciones de proteina fueron calculadas a un término medio para grupos de cinco edades: 2 recién nacidos, 11 infantes 6 a 46 semanas de edad, 10 niños de 1 a 4 años de edad, 17 niños de 5 a 11 años de edad y 14 niños de 13 a 17 años de edad. Los valores medios para la mayor parte de las fracciones de plasma concordaron bien con resultados publicados anteriormente para adultos y niños normales; pero se notaron cambios con la edad en la concentración relativa de algunos de los componentes.

El porcentaje de albumina disminuyó de la infancia a la media-niñez, ocurriendo los valores significativamente más bajos en niños de 5 a 11 años de edad. Sin embargo, las cifras para la concentración absoluta de albumina en gm./100 ml., calculada de valores determinados quimicamente para una concentración de proteina total, no mostraron disminución significativa en albumina para este grupo de edad.

El porcentaje y la concentración absoluta de α_1-globulina fueron significativamente más altos que el nivel adulto normal en infancia y disminuyó gradualmente con el aumento en edad.

No se notaron cambios significativos con la edad en los valores de porcentaje para α_2-globulina, β-globulina y fracciones fibrinógenas.

El porcentaje y la concentración absoluta de γ-globulina disminuyó de valores generalmente altos en el infante recién nacido a los valores generalmente bajos en infancia, después aumentaron gradualmente con la edad hasta alcanzar el nivel adulto normal (8 a 11%) en media-niñez, 5 a 11 años de edad. Se cree que estos cambios están relacionados con la pérdida de la inmunidad pasiva recibida por el infante de su madre, y al desarrollo de la inmunidad activa y a la acumulación de anticuerpos de inmunizaciones y a la exposición a infecciones durante la niñez.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

THE current issue contains two communications: The first is by Dr. Ronald S. Illingworth on the British National Health Service and the second is by Dr. Donald Patterson on the British Columbia Hospital Insurance scheme. Dr. Patterson was formerly Consulting Physician to the Hospital for Sick Children, Great Ormond Street, London, England, and is now Pediatrician-in-Charge, Health Center for Children, Vancouver General Hospital, Vancouver, B.C.

Dr. Patterson has also provided the following introductory remarks to the first communication:

"Ronald S. Illingworth is one of the younger English paediatricians and holds the title of Professor of Child Health at Sheffield University, a chair established in 1947. His early medical education was in Leeds, and he was trained in paediatrics to a great extent at the Hospital for Sick Children, Great Ormond Street, London. He is a member of the British Paediatric Association and a Fellow to the Royal College of Physicians, London, England. He held a research post at Oxford and was in the army as a medical specialist throughout the war, and rose to the rank of colonel. He has contributed many important papers while in the army, a particularly outstanding one on the diagnosis of smallpox. In paediatrics, his writings on prematurity, acute haemorrhagic nephritis and a number of other paediatric subjects are well known to British paediatricians.

"Illingworth's paediatric service in Sheffield is a delight to visit. He has revolutionized the Children's Hospital there and with a considerable staff of full time workers much research and teaching is taking place. Illingworth himself is a tremendous worker, definitely Spartan and quite tireless. He is most outspoken and has no use for humbug.

"I have no idea what his views are regarding National Health Service, as he has not

discussed them with me. I thought, however, that his point of view coming from outside the London area, namely, the middle portion of England, would be interesting and refreshing and give at least one slant on the National Health Service."

FIRST YEAR OF THE BRITISH NATIONAL HEALTH SERVICE

By R. S. ILLINGWORTH, M.D., F.R.C.P., D.P.H., D.C.H.

THE introduction of the comprehensive Health Service on July 5, 1948, was rightly described by the *Lancet* as the biggest operation ever known in medicine.

The operation ran smoothly and without fuss, no major difficulties arising. By the end of six months, 95 to 98% of the population had chosen their doctor, while 86% of the general practitioners and 91% of the dentists had enrolled in the scheme.

NEED FOR A COMPREHENSIVE HEALTH SERVICE

There is no doubt at all that the country wanted a comprehensive health service. This was clear long before the present socialist government came into power. The previous government (coalition) had attempted to evolve such a service, but the general election put a stop to negotiations then in progress. The need was obvious. For some years there had been a growing dissatisfaction with the medical services. The National Health Act, which originated in 1911, did not provide medical care for the wives and families of those insured, nor did it provide anyone with free specialist consultations, except in midwifery, or with free hospital care, except in the case of poverty. Illness was a serious drain on the pockets of the lower and middle classes. Doctors' bills were heavy, especially in sparsely populated country districts, and there was a natural tendency to call in the doctor only when the illness was advanced. The distribution of practitioners, and particularly of specialists, was uneven: general practitioners naturally tended to choose the pleasant towns and country places, leaving the unpleasant industrial towns with far too few doctors. Specialists were almost entirely confined to the cities which possess teaching hospitals and large areas possessed no specialist at all in such subjects as paediatrics. Domiciliary specialist consultations, except in the case of midwifery, were available only to those who could afford them. The Health Services, excellent as they were, were insufficiently coordinated and lacked integration. There were two separate and distinct hospital systems: the voluntary hospitals, which were financed by voluntary subscriptions and organisations, and the municipal hospitals, which were financed and controlled by the local authority, such as the city. They lacked correlation, with consequent wasteful duplication of staff and equipment. Voluntary hospitals, which tended to be more popular with the public, had tremendous waiting lists, while municipal hospitals had empty beds and no waiting lists at all. A considerable proportion of voluntary hospitals were falling increasingly into debt. Many of the smaller hospitals were inadequately staffed and badly equipped, and in some cases their local committees lacked vision and failed to recognise their needs.

NATIONAL HEALTH ACT

It was with this background that the National Health Act came into operation on July 5, 1948. Under this Act, the Ministry of Health provides full medical care, includ-

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ing full practitioner, specialist, hospital and convalescent services, and all necessary appliances, free of charge to every man, woman and child in the country. All have a free choice of doctor and can change the doctor if they wish. The cost of travel to hospital is refunded if the distance is over 15 miles, or less in case of need, and ambulance services are supplied. All hospitals have been taken over by the Ministry, although teaching hospitals retain a considerable degree of autonomy. The vast majority of specialists, dentists and practitioners have chosen to enroll in the scheme.

The Minister of Health is advised by a Central Council which includes representatives of all the leading medical bodies, such as the British Medical Association. The country is divided into regions, each with a university teaching hospital in the centre, which is controlled and staffed by a "Board of Governors." The nonteaching hospitals are placed under the "Regional Boards." These Boards, which are unpaid, are appointed by the Minister of Health and are composed of persons, lay and professional, who are intimately concerned with hospitals and their administration. The appointments have for the most part been commendably nonpolitical. They include doctors nominated by the University, teaching hospitals and other bodies, and representatives of the Local Authority. Each Board has various subcommittees, many of them purely professional. The Regional Boards, for instance, have subcommittees of all the various specialties, such as paediatrics and dermatology, whose duty it is to advise on all matters pertaining to that speciality in the entire area. They have to advise on the grading of specialists in the region, on the adequacy of hospital accommodation and staff in all parts, including the outlying ones. The specialists on the staff of teaching hospitals inevitably play a major rôle on these committees and boards.

The Local Authority is responsible as before for the maternity and child welfare, school medical services, and midwifery services, for the provision of home helps, the home nursing service, immunisation and ambulance services. The local executive council in each area concerns itself with the practitioners, dentists and pharmacists.

Effect of the Health Act

There has been no comprehensive evaluation of the first year of the Health Service. The opinions expressed below are those of the writer. They are based on his own observations as a physician to a children's hospital and a full time member of a university staff. They include impressions obtained from discussions with general practitioners and others whose opinion he respects.

Effect on the Child

The service is probably leading to the earlier treatment of the child because there is no longer a fee for attendance at the surgery or for a visit to the home. Practitioners have remarked that they now see less advanced disease in children. Cases of pneumonia, rheumatic fever or gastroenteritis are seen earlier. In many cases disease can be detected before it has produced symptoms, because children are taken to the doctor for a routine check-up.

Another advantage to the child is the fact that the practitioner can always obtain a specialist opinion without extra cost to the parents. Free dental and ophthalmic treatment is clearly of advantage to the child.

The reviews of the regions are leading slowly to a better distribution of specialists and to a better staffing of hospitals. They may lead to a pooling of resources and therefore in some cases to better accommodation, particularly accommodation of special type,

such as that for rheumatic fever and orthopaedic conditions. In this city, for instance, a rheumatic fever hospital school, previously available only for children from the city of Sheffield, is now open to any child from the area, and extensions are being planned to meet the extra demand on beds.

The service has led to certain disadvantages for the child. In places where there are not enough doctors, surgeries have become severely overcrowded and patients have to wait in queues for attention. The doctor is then unable to give sufficient time to each patient, and his examination may be inadequate. This applies partly to overcrowded areas where there are too few doctors and partly to the particularly popular doctor, who has enrolled the maximum number of patients allowed (4,000) in order to obtain the largest possible income at the cost of proper service to his patients; for every doctor has the right to restrict the number of patients he enrolls. This disadvantage should, however, be counterbalanced by the increased ease with which the doctor can obtain a specialist opinion for his patient. It is surprising, therefore, that the service has not, in fact, led to an increase in children's outpatient attendances in hospitals.

The tremendous demand for dental and eye treatment has also led to difficulties in the form of long waiting periods for the attention needed. This difficulty, however, is probably only a temporary one. There was a real need for free treatment, and, when the demands of those who previously could not afford treatment have been met, the waiting periods should gradually disappear.

The essential question is whether in general the patient has lost or gained from the service. The answer is that he has lost little. It is hoped that the difficulties, such as queueing and inadequate attention in some surgeries, will be overcome; in any case they are small compared with the advantages of free and earlier treatment with specialist advice where necessary. The standard of work in most practices is unchanged. There is certainly no ground for suggesting that the standard of hospital work is any lower than it was in the past. The standard of the work of specialists is unchanged: the child is treated by the same surgeons, the same specialists, as before.

Effect on the Doctor

The General Practitioner

The salary of the general practitioner seems to be reasonable, except in certain rural areas. Admittedly some with small practices have lost, but others have gained. He is paid the equivalent of $3.25 per patient per year and may take up to 4,000 patients on his list. This would give an income of $13,000 a year, out of which, of course, he has to cover expenses in connection with the running of his practice. In addition, he is paid extra for maternity work, mileage for long journeys to outlying houses, for dispensing drugs (in country practices), attendance on Boards and Committees, and for the training of an assistant. He is given a special inducement fee for settling in certain industrial areas. He may charge fees for patients who have not enrolled in the service. He no longer has to worry about bad debts.

Some doctors say that they have less night work because they tend to be called in earlier. A conscientious doctor is helped by being able to call in a specialist more easily, without having to consider whether the patient can afford it.

Some practitioners, however, in parts where there is a shortage of doctors, have been

severely overworked. Others have been overworked because they unwisely took on more patients than they had time to treat. A minority of patients have abused the service. They are determined to get all they can out of it and make excessive demands on the doctor's time and unnecessary requests for drugs and appliances. These abuses have received much publicity, but they are not general. There is little evidence of abuse in those districts where general practitioners, before July 5, 1948, gave a good service which the patients had learned to use wisely.

The doctors have certainly a tremendous number of forms to fill in. This is not a fault inherent in the Health Service. It existed long before the Health Act. It is due to the increase in social insurance and services financed by the State. It is also due in part to the material and financial shortages occasioned by the war. Accurate record keeping is essential wherever public moneys are involved. The burden of form-filling is, however, excessive, and there is great need for limitation and rationalisation of these forms.

Practitioners have to a considerable extent lost the freedom of settling in a practice of their choosing. They cannot settle in a practice where they wish unless there is a need for a doctor in that area, or unless they stay outside the service altogether, as they can if they so desire. On the other hand, they will be given a special inducement, in the form of additional payment, if they will settle in an industrial area where there are insufficient doctors. The doctor has clearly lost freedom in this important matter. He certainly does not lose financially, because if he goes to an area with too few doctors his income will inevitably be a good one. It can hardly be denied that this "direction" of doctors is to the advantage of the community and is inevitable in some degree if the government is to fulfill its pledge to provide a reasonable standard of medical service in all parts of the country.

The practitioner has above all gained the opportunity to develop a true family practice. In the past the father might go to one doctor, under the National Health Insurance scheme, and the mother and children to another. Already an increasing number of families attend a single practitioner. He has not lost freedom of speech and publication, freedom to treat the patient as he thinks best, or freedom to choose the specialist whom he thinks the most suitable. He has a reasonably assured income. His greatest lack is premises and equipment and opportunity for close collaboration with his colleagues. These must await the building of the Health Centres, which has been held up by shortages brought about by the war. These are essential for the improvement and efficient working of family practice.

The Paediatrician

It is only in recent years that paediatrics has become widely recognised as a speciality in this country and few paediatricians, who did not also treat adults, were able to make a reasonable income. There were consequently no paediatricians in cities or towns without a university. Even in university towns it was extremely difficult to make a living. The Health Act, by providing a salary, has made it possible to place paediatricians where they are required, whether in teaching hospitals or elsewhere. Already several senior paediatricians have been appointed and many more appointments are expected in the next few months.

The salary of full-time consultants appointed at the age of 32 commences at $6,800 and rises to $10,000. These salaries have only recently been fixed but they are paid in

retrospect to July 5, 1948. Also fees for lectures to nurses and students and certain travelling expenses are allowed. Part-time specialists fare rather better. They are able to earn up to 9/11 of the income of the full-time specialist, mostly for work for which they were previously unpaid, and in addition they receive fees for private consultations. Full-time university professors, who also act as consultants to hospitals, receive comparable salaries, but they will only be paid in retrospect to April 1, 1949—an unfair distinction. All specialists, whether full-time or part-time, including university professors, are entitled to awards for special merit, those awards being recommended by a special committee. Four per cent of all specialists will receive an additional salary of $10,000, 10% will receive $6,000, and 20% $2,000. There will inevitably be much heart-burning about those awards, for it is exceedingly difficult to allocate them fairly. In general one must admit that the salaries are reasonable. They have certainly enabled several paediatricians to perform essential work which would otherwise not have given them a living.

The Health Act has inevitably given specialists, particularly those attached to Universities and teaching hospitals, a great deal of committee work. This causes a lot of grumbling, but it cannot be denied that the committees are necessary. The heads of departments in universities and consultants in teaching hospitals are privileged to play a vital and responsible part in the efficient running of the Health Service for the benefit of the community. They are responsible for advising the Boards about the accommodation and staffing required to give a comprehensive specialist and hospital service in the region.

The amount of hospital work done by paediatric specialists has not been changed by the Health Act. The vast majority of specialists in the country are working part time in the Health Service and are engaged in the remainder of their time in private consultant practice. It is difficult to say whether paediatricians as a body have had a reduction or increase in their private work.

One serious difficulty, which has to be faced in any comprehensive Health Service, is the grading of specialists. It is next to impossible to give an adequate definition of a specialist. Higher degrees and years of experience in a special subject certainly do not in themselves make a man competent in a speciality. A man with only two years' experience of paediatrics may know a great deal more than one who has had five years' experience. The grading committees, composed of senior university and teaching hospital staffs, had a thankless task in grading men and deciding whether they were to be considered specialists. If they did not think that they were of full specialist status, they had to place them in the appropriate grade of trainee specialist in order to fix their salaries. Inevitably some considered themselves to be specialists and the committee thought otherwise. Every possible attempt has been made to perform the task fairly, but some dissatisfaction is inevitable.

In general, it is difficult to see any way in which paediatric specialists have lost from the Health Act. Many have gained financially. Many have more committee work. None have lost freedom. All can look forward to a great extension of the paediatric services of the country.

Specialists in Training

The salaries paid to the junior staffs of hospitals have always been inadequate and the recent rises in the cost of living have caused grave financial embarrassment to many young doctors, especially married ones who have served in the Forces. The grading of all

these men has been a big undertaking, and the long delays in fixing their salaries have caused great difficulties and uncertainty. Furthermore many of them had been waiting for the new specialist posts to which the Health Act was bound to give rise. The Board's task of sifting and coordinating the reports of the special advisory subcommittees in all the various specialties to give a really comprehensive and integrated plan for the whole region is a big task, and that task has been constantly hampered by the need for strict economy necessitated by the tremendous cost of the Health Service and by the financial state of the country. In consequence there has been much delay in making the expected appointments; only a few have been made to date, but many more are expected in the next few months. Meanwhile the ex-service specialists in training have suffered serious financial hardship.

The salary of junior hospital doctors has now been fixed. House officers in the first post after qualification are to be paid at the rate of $1,000 a year, $1,200 in the second post, and $1,400 in the third, in each case with board and lodging included. The posts are normally held for six months each. The junior registrar begins at $2,680 a year: after not less than two years, he receives $3,000, rising to $3,560: after not less than four years he receives $4,000, rising to $5,200 dollars. There is an intervening grade between this post and that of specialist. In addition he is entitled to certain expenses, such as those caused by attending selected scientific meetings. All the salaries are payable in retrospect to July 5, 1948. The Health Act has, therefore, considerably increased these salaries—and so has made it easier for young men to specialise. It has made no difference at all to the work they do or to their freedom. It has increased the demand for these men, because of the deficiencies in hospital staffs revealed by the regional surveys.

Preventive Health Services

The salaries of the doctors in the Preventive Health Services, such as the School Medical Service, have not risen in proportion to those of other branches of medicine, a fact which has caused much justified discontent. It is now almost impossible to secure a school dental officer because of the large incomes which can readily be made in private practice. It is too early to say what answer will be found to this problem.

Dentists

The payment of dentists is on a different basis from that of doctors, for they receive a fixed sum for each item of work done. The Minister was wrongly advised by the Dental Profession on the amount of pay which they should receive, for their earnings have proved to be excessive, and out of proportion to those of others, such as practitioners and specialists. It was recently shown that 21% of the dentists in the Service were earning over $24,000 a year, 60% over $14,400 and 82% over $9,600.

The quality of work of some dentists has suffered, in some practices because of a severe shortage of dentists in the area, and in other practices because the dentists, in order to obtain the largest possible income, undertook far more work than they could manage without a lowering of standards. Many good dentists, in order to have time to give proper treatment, have refused to treat under the scheme any who were not their patients before July 5, 1948. The latter are therefore given the same care and attention as before, but free of charge.

Effect on the Hospital

Most of the voluntary hospitals (hospitals which depended on voluntary subscriptions) were gravely in debt at the time they were taken over and in many cases the debts were steadily increasing. In addition most of them were too small and of antiquated design, so that they had extensive plans for new buildings involving millions of pounds. Some solution to their financial problem was therefore essential. On July 5, 1948, the Ministry of Health took over all the hospitals, with their debts and assets.

The coordination of the hospital services, both voluntary and municipal, which has resulted from the transfer, is unquestionably of advantage to the hospitals. Some small hospitals have benefited from the new availability of special apparatus possessed by the larger units. The need for reorganisation of facilities and better staffing in a hospital has often been readily seen by the committee of specialists appointed by the Board, while the local committee had been blind to the need. In some cases, where there were two or three hospitals in the town, each with small inadequately staffed children's wards, the children have been concentrated in the one hospital with the best accommodation, thus making better nursing possible. Many small redundant infectious disease hospitals have been closed, as a result of the regional planning, making the buildings so released available for other purposes, such as orthopaedic conditions and rheumatic heart disease. Prior to the Health Act many of the hospitals under the local authorities were available only to children from the particular town in which these hospitals were situated. They are now open to anyone and this makes it easier to get cases into hospital. There is good liaison between the teaching and nonteaching hospitals; many specialists serve on both.

One might have expected that the more ready availability of specialists and the overcrowding of some doctors' surgeries would lead to overcrowding of hospital outpatient clinics. In fact there has been no change in outpatient attendances of children, as far as the writer can determine. In the Sheffield Children's Hospital, for instance, there have been 11,000 new outpatients in the last 12 months, as compared with 12,200 in the 12 months ending July 5, 1948. The fact that all medicine can be obtained through the doctor without charge makes it easier to make the outpatient department purely a consultation clinic, as it should be. There is no need to allow the poor to attend repeatedly merely to obtain their medicine.

On the other hand, it is undeniably more difficult to get things done. Recommendations involving the expenditure of over $1,000 have to go through at least one additional committee and be approved by the Board. All hospital accounts are subject to careful scrutiny by agents of the Minister and the urgent need for economy is constantly being stressed. There is no doubt that this economy campaign has put a severe brake on progress; it has been the greatest single obstacle in the whole health service. One must remember that the voluntary hospitals were for the most part gravely in debt before they were taken over, and the enormous cost of the Health Service must constantly be related to the financial position of the country as a whole.

Appointments of staff above the level of House officers, which used to be entirely in the hands of the hospital concerned, are now made by a committee of the Board, on which, of course, the hospital concerned is well represented. In the appointment of full specialists, a senior specialist from a different region is co-opted to the appointments committee. This sounds a cumbersome method, but it has its advantages—in avoiding

nepotism and wire-pulling, and so enabling the best man to be appointed, whether or not he happens to be a relative of someone on the staff.

There is no doubt that the administrative staff is involved in much more paper work than previously and has had to be increased accordingly.

There is certainly not the slightest ground for suggestion that the quality of hospital work has deteriorated in any way whatsoever.

Effect on Medical Schools

The Health Act has had little effect on these, and teaching continues as before. The better liaison with the nonteaching hospitals has in some cases enabled a greater amount of clinical material to be available for teaching. There has been no falling off in the number of applicants for admission to the medical schools. Many have tried to suggest that the Service would be so bad that it would lead to students seeking other careers. There is not the slightest ground for such a suggestion. Those who want to become doctors for the right reasons, and with a desire to be of real service to the community, are not going to be put off as easily as the propagandists seem to think.

Effect on the Country as a Whole

It is impossible to assess the effect of the Service on the health of the country. The health of the country was improving long before the Health Act came into being, and it is foolish to ascribe the record low infant mortality rate (34 in 1948) or maternal mortality (1.01 in 1948) to any effect of the new Health Service.

The majority of the people have no idea how the Health Service is being financed. They do not realise that nine tenths of the total cost is paid for by general taxation, of which the tax on tobacco and alcohol forms such a large part, and one tenth by the National Insurance contributions which are deducted from the payroll. Everyone pays for it and pays a lot, but it does give security—security against the devastating effect of illness on the purse.

Difficulties and Criticisms

It must be borne in mind that negative criticisms are likely to receive more publicity than positive ones. It is in the nature of many to be negative rather than positive, destructive rather than constructive, and the negative tend to be the more vociferous and to write more to the Press. It is quite impossible, therefore, to obtain an accurate picture of medical opinion on the Service from reading correspondence in the medical journals.

There has been much superficial and malicious criticism of the Health Service. Some of it has been of a political nature and some of it emanates from a dislike of the personality of the Minister. It would be idle to expect all doctors to agree about the details of any scheme which provides comprehensive medical care to a community. Doctors are human, and it is natural that older members of the profession, who had built their practices through years of work, should object to radical changes. It can hardly be denied that in their public campaign some members of the profession have shown a lamentable ignorance of public need and criticism, and a regrettable concentration on self interest rather than on the interest of the community. Many doctors, however, in their public speeches and in correspondence in the Press, have made valuable constructive suggestions, which eventually led to changes of advantage to all.

Many doctors have written to complain about the loss of private practice. That is unfortunate for the doctor, but not for the patient. Others have complained about the number of patients seen because of trivial complaints or for a routine check-up. These criticisms are a serious reflection on the teaching of the medical student and on the attitude of the doctor to preventive medicine.

The magnitude of the operation was such that initial difficulties and miscalculations were inevitable. The extent of the need for spectacles was not accurately known, and the demand has been such that it has absorbed an undue proportion of available funds. Payment to pharmacists and dentists has been overgenerous. Such mistakes can and will be remedied.

There has been considerable wastage of money as a result of overprescribing. Seventy-five million prescriptions were dispensed in the first six months of the Service. Bad doctors find it easier to give the patient a bottle of medicine than to cure his anxieties, insomnia and fears by genuine sympathy and sound advice. It need hardly be added that a considerable number of the medicines prescribed have no pharmacologic action. Successful advertising by drug firms has led many to prescribe highly expensive proprietary preparations instead of equally effective and much less costly drugs in the Pharmacopoeia. This overprescribing is a reflection on the training of the medical student.

Some patients have undoubtedly abused the service and demand bottles of medicine or appliances which are unnecessary. It is difficult to see how such abuse, which depends on the character of the individual, can be prevented.

Another difficulty is the shortage of doctors and dentists. This has been the essential factor which has led to a deterioration in the quality of work in some industrial practices. No doctor should be allowed to have 4,000 patients on his list, as he is now, for it is impossible to give adequate attention to that number.

All doctors, quite naturally, fear loss of freedom by an increase in the powers of the Boards and of the Minister. The danger is a real one. The Boards have a great deal of power. One can only hope that the Boards, the Central Advisory Committee, the professional organisations and public opinion will prevent encroachments on the freedom of the doctor unless it is quite definitely in the interests of the community.

The lingering doubt, possessed by all thinking men, is whether the country can afford the service. The estimated cost to taxpayers next year is $1,040,000,000. It is significant that this is about one third of the cost of defense expenditure. One difficulty is that salaries are rising, and there is a tremendous building programme which will cost millions of pounds, to be put in hand as soon as materials and finances permit. It seems inevitable that the cost of the Service will continue to increase. Taxation is already excessive, and one of the highest in the world, and it is difficult to see how it can be further increased.

It is far too soon to make a proper evaluation of the Health Act. The opinions expressed are those of the writer. He is fully aware that in a year or two those opinions may have completely changed.

DEAR DR. HARPER:

Enclosed are my remarks on the British Columbia Hospital Insurance scheme, which has only been going for the last seven months. It is really too early to say much, but Ned Park was insistent that it appear in PEDIATRICS.

The Government of the Province of British Columbia passed a Hospital Insurance

Act in 1948, and on Jan. 1, 1949, Hospital Insurance was introduced. There can be no question that it is definitely a hospital plan only and not a health scheme. There was never any intention of including medical services at this time. It does not provide for payment of doctors' bills or other medical expenses. The treatment of the mentally ill, patients in tuberculosis sanatoria, and infirmary and venereal disease treatments requiring institutional care are not included in the benefits. They are, as at present, dealt with under the provisions of various acts governing these institutions.

Premiums have been set at a rate which the average person can pay. For a single person 16 years of age and over the annual premium is $15. For the head of a family with one dependent it is $24, and for the head of a family with more than one dependent it is $30 a year. While many prefer to pay a full premium at one time, provision has also been made for families and individuals wishing to pay by installments. They have the choice of six monthly or two half yearly payments. One third of the province's population is paying monthly premiums on a payroll deduction plan.

Prior to the introduction of Hospital Insurance, from one third to one half of all patients entering hospital were unable to meet their hospital bills and the Government was required to make good this loss in order to keep hospitals solvent. Hospital Insurance should result in two benefits. First, hospitals will be relieved of the losses which now result from the inability of many people to pay hospital bills. Hospital Insurance is making payments to hospitals on a day rate, based on actual operating cost of the individual hospital, and in the future no hospital should have an operating deficit. Secondly, hospital costs will be spread over the whole community, making everyone eligible for the same service whatever his income.

What are the services offered under Hospital Insurance? They include public ward accommodation, meals and special diets, ward nursing care, operating and case room facilities, as well as roentgenogram and other services when available. Under other services are included laboratory investigations. There is no age limit, no discrimination against persons with pre-existing conditions and no waiting period for maternity cases. Doctors' medical and surgical fees while the patient is in hospital are not paid for under the scheme.

Those who want special nursing care, or the use of private or semiprivate rooms must pay the difference between the rate paid to the hospital by the service and the private or semiprivate room rates. The needs of those already receiving Social Assistance from the Provincial Government have been covered; their Hospital Insurance premiums have been paid by the Government and they have received their Hospital Insurance cards.

There has been much criticism of the scheme by the public, who claim that there are insufficient hospital beds to meet the demand. On the other hand, in the Vancouver area there are five beds per thousand people, which compares favourably with the minimum standard of 4.5 beds per thousand recommended for large urban areas in the United States. Writing as I am late in July, it appears that one citizen in five of the Province will have made use of the hospitals under this scheme by the end of the first year. Remember that a number of people saved up their illnesses so that they could make use of the hospitals under the insurance scheme. I note that there are about 6,000 beds in the Province which come under the plan and that the whole population of considerably over a million people are participating. This service has paid bills totalling more than four million dollars already and it is interesting to note that some of the largest accounts

which have been approved have been anywhere from five hundred dollars to one thousand dollars. Efforts are being made to increase hospital accommodation.

What effect has Hospital Insurance had on the ordinary practicing physician, particularly on paediatricians? As far as I can gather it has been definitely beneficial. Competition for hospital beds is keen, but once a patient is in hospital roentgenograms and laboratory investigations are made without any fear of running up a big bill on the patient, as they are included, and the average patient has therefore more of his money left to settle the doctor's bill than he ever had before. Let me reiterate that doctor's fees are not covered by Hospital Insurance. This remains a private arrangement, as always, between the doctor and his patient, and it is only hospital accommodation and services which are covered by Hospital Insurance.

Will the Province be able to continue to finance this hospital insurance scheme? That, of course, is something I am not in a position to answer, but everyone connected with the service appears to be quietly confident that they are on sure financial grounds and they do not appear to be in the least worried.

(Signed) DONALD PATTERSON, M.D.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

IN KEEPING with the recently adopted policy of reviewing in this column state and local, as well as national, events and trends dealing with the health and welfare of children, it is timely to call attention to action resulting from the Academy's Study in New York State. The following is quoted from an article by Dr. George M. Wheatley under the title of "Study of Child Health Services . . . a challenge to action":*

"With the completion of the New York State Study, we now have for the first time information for our State as a whole on the total amount, distribution, and character of all health services presently available to children as well as knowledge of the professional training of those who render these services. Now that we have this report with its wealth of significant data, how can we best make use of it? It will serve its primary purpose if it is used at the state level by medical, dental, public health, and welfare authorities for the development of long-range plans as well as for immediate action. Community groups throughout the State can make use of the report to study and compare, and, where indicated, work to improve their own health resources for children. For individual physicians, the study presents a responsibility and a challenge. Many practitioners will recognize similar conditions in their own counties. In private practice, in hospital and clinic affiliations, and because of important position in the community, the physician has the opportunity and the means of making a tremendous contribution to the health of children.

"New York State compares favorably with the rest of the nation in the kind and amount of medical services it provides its children; in nearly all respects it ranks well above the national average. But tremendous disparities do exist within the State, and much remains to be done before we attain the goal of making good medical care available to all our children. Two things stand out above all others as 'musts': (1) Steps need to be taken to improve the medical training of all physicians—general practitioners and pediatricians alike—to give them the best possible preparation for child care; (2) Children in isolated areas should receive the same opportunities for good care that are available to those near medical centers.

DISTRIBUTION OF MEDICAL SERVICE

"Upstate New York has about half the number of physicians per child population in relation to the Greater Metropolitan group of counties. While transportation facilities enable a substantial number of rural children to go to physicians in these more thickly

* Wheatley, G. M., Study of child health services . . . challenge to action, Health News **26**: 3, 1949. Published by New York State Department of Health. Quoted with permission of author and publisher.

populated centers for care, nevertheless, the study shows that children outside the Greater Metropolitan group of counties receive on the average 30 per cent less medical care from private physicians. They receive, in proportion to their numbers, about the same amount of hospital care, but only about one-tenth of the clinic care that is available to children who have access to services in the Greater Metropolitan area.

"In modern medical practice, it is impossible to divorce hospital services from the personal services of the physician. The *well-trained physician* depends upon easy access to a good hospital for satisfactory treatment of patients. Consequently, any recommendations which aim to improve the distribution of medical service in the State must consider hospital facilities as well as individual medical service. More physicians will be encouraged to settle in the counties where they are most needed if they have access to good hospital service.

"It is recommended that hospitals in outlying counties agree to an exchange of services with a medical center in a metropolitan area. Such an agreement should lead to improved clinical service including better pediatric care and educational opportunities for the hospital staffs in the small communities.

"The Hospital Planning Commission's proposed regional organization of hospitals and community hospitals into primary, secondary, and community hospitals according to their facilities and population served should be implemented to strengthen the system of hospital care and bring more services to rural counties.

Dental Care

"The children of our State are receiving on an average only about half the dental care required. This deficiency is most evident in those counties outside of the major cities. These areas lack both private dentists and clinic facilities.

"Efforts should be made to encourage dentists to settle in these localities. More emphasis should be put on dental education in the schools to encourage more frequent visits to dentists. Caries prevention through a topical sodium fluoride program is recommended for all children. But the annual increment of caries is so great, especially in areas where there is now insufficient dental service, that additional treatment facilities for these areas and inclusion of school-age children in the program are recommended.

"Opportunities should be created to provide more undergraduate and postgraduate treatment in pedodontia. Where possible, cooperative arrangements should be developed with departments of pediatrics of medical schools so that dental students can learn the relation between dentistry and children's diseases. It is further recommended that pediatric services should provide opportunities for dental students to learn pediatric dentistry.

Pediatric Education of the Practitioner

"We learn from the data that the general practitioner carries the bulk (70 per cent) of the load of health services to children, both sick and well. In contrast to this volume of care, relatively little time is given to pediatric training of the physician in medical school and most of the emphasis in this undergraduate period is on the care of sick children. In their hospital training, a third of the general practitioners reported little or no service in pediatrics. One reason for this lack of hospital experience in pediatrics is due to the dearth of internships as well as absence of pediatric services in many fairly large hospitals. Furthermore, many practicing physicians are not permitted to care for their

patients in local hospitals. Because of these findings, the following recommendations are made:

"*Undergraduate Education*—Medical schools should strengthen their pediatric teaching to include more attention to the preventive aspects of pediatrics and to stress human relationships as a preparation for private practice.

"*Hospital Training in Pediatrics*—Those hospitals of over 100 beds with no intern staff should have house staffs. Where such hospitals cannot provide an adequate pediatric experience for interns, the staff should be rotated through a pediatric teaching center for at least one month. Provision should also be made to send interns with pediatric training from pediatric services of the larger teaching centers to general hospitals to assist in the development of pediatric units and to bring better pediatric techniques into these hospitals.

"*Postgraduate Education*—The excellent medical education program sponsored by the Medical Society of the State of New York through its Council Committee on Public Health and Education in cooperation with the State Department of Health should continue its emphasis on pediatrics, with particular attention to health supervision, including growth and development and mental health. This teaching should be done through: (1) Sponsoring pediatric clinics in local hospitals; (2) Stimulating medical centers to offer short pediatric courses, particularly to encourage practitioners to attend from those communities where there are no pediatricians; (3) Fostering the development of group consultation service, particularly in communities where there are no pediatricians; and (4) Use of child health conferences for graduate and undergraduate teaching of normal growth and the care of the well child.

"New York ranks high in the volume of health supervision compared to other states. Of equal, or perhaps greater, importance is the fact that so many parents are now looking to their own physicians, whether pediatrician or general practitioner, for this service. Health supervision appears to be continued over a longer period in the metropolitan areas than in the outlying sections. The failure of families to continue with this supervision beyond the first two years of life presents a problem.

"Health supervision depends upon the family's interest, willingness, and ability to continue to bring the child for medical counselling; it also rests in large measure upon the physician's skill in making these health guidance visits profitable to the family. As the child matures, immunizations become less important, and accidents, emotional development, nutrition, and other problems associated with the growing child's reaction to his environment are often the paramount reasons why the family looks to the physician for help.

"It is recommended that: (1) Medical education programs for general practitioners, both graduate and undergraduate, stress normal growth and development as well as the health and safety problems which arise in the pre-school years; (2) More facilities for well-child supervision be developed in the Isolated and Semi-Rural counties; and (3) In health education of the public, the importance of continuing children under medical supervision beyond the second year should receive greater emphasis.

Pediatric Units in General Hospitals

"Thirty per cent of hospital births occur in institutions which do not have separate facilities to segregate suspected or ill newborns from well babies. Forty-five per cent of

hospitalized children are admitted to hospitals which do not separate sick infants from sick older children. About 20 per cent of hospitalized children go to institutions where there is no resident staff.

"It is recommended that: (1) General hospitals of 100 or more beds provide separate pediatric units; (2) Well newborns be separated from sick newborns; and (3) Infants and older children be separated. In general, this is in accordance with the provisions of Regulation 35, Chapter II, of the State Sanitary Code, with which this Committee is in agreement.

"As plans for the new hospital construction are developed through the State Hospital Planning Commission, adequate pediatric facilities for newborn and other facilities should be included.

"*Premature Services*—Hospitals reported caring for 10,743 premature infants in the study year, yet about 60 per cent of the hospitals caring for prematures have no separate nursery. It is considered impractical for hospitals which never have more than four prematures at any one time to provide the elaborate facilities necessary for adequate care.

"It is recommended that: Only those hospitals where 1,000 or more births occur each year provide their own special premature nurseries. The smaller hospitals should send their prematures to the specially equipped hospitals. Plans should be developed to transport premature infants in incubators to the specially equipped hospitals.

"*Poliomyelitis*—Actual treatment for poliomyelitis patients was available in only 29 per cent of the total hospitals reporting. About half of the larger hospitals (250 or more beds) reported admitting cases for care.

"More general hospitals, especially the larger ones in strategic areas of the State, should be prepared in epidemics to provide not only diagnostic facilities but care for the poliomyelitis patient.

"*Training of Nurses in Pediatrics*—The lack of organized pediatric services in so many of the hospitals of the State limits the preparation of nurses in pediatrics. There is also a lack of opportunity for public health nurses to secure preparation in the general principles of pediatrics. With the development of a program for the care of premature infants, there will be need for intensive preparation of well-qualified graduate nurses for instructional preparation in connection with such programs.

"To improve the training of nurses in pediatrics, it is recommended that: (1) Pediatric units be developed in those hospitals of 100 or more beds which do not now have them; (2) Nursing personnel be exchanged between the larger teaching hospitals with pediatric services and pediatric hospitals; and (3) Nursing schools in pediatric hospitals be strengthened for the purpose of postgraduate teaching of pediatrics to nurses.

Community Health Services

"*County Departments of Health*—At the time of the Study, only six county health departments existed, comprising about 18 per cent of the upstate total population. The half dozen basic services of public health—vital statistics, communicable disease control, environmental sanitation, public health laboratory service, maternal and child health, and health education—are widely accepted by professional and governmental authorities as important functions of local government. These services are essential to the development of other community health services for children.

"Local public health units with a full-time qualified public health staff should be

established as rapidly as possible as the first step toward narrowing the disparity between community child health services in rural and urban areas.

"*School Health Service*—In spite of New York's comparatively large number of school health personnel, there are school districts, notably in rural areas, where public health nursing and dental hygiene services are not available. Medical and nursing supervision of the program at the community level is inadequate. Yet this is perhaps the most important factor in improving the quality of the service. County health departments can and should provide school nursing and dental hygiene services. Professional supervision at the community level should also be provided by the county health department. School health service should be supervised at the local level by county health departments as these local health units are developed.

"*Mental Hygiene*—In the larger cities of the State there are a number of good mental hygiene services which operate in connection with the pediatric services of the hospitals, schools, and clinics. Nevertheless, the waiting lists at all of these places are very long. In rural areas these facilities of the child guidance clinics are grossly inadequate to meet the need.

"Clinic facilities for mental hygiene are needed, especially in the localities outside of the larger cities of the State. It is even more important that the principles of mental hygiene be stressed in the education of both physicians and nurses and other health workers who serve children.

"*Handicapped Children*—According to the data it appears that most of the orthopedically handicapped children are receiving some clinic care either through official or voluntary agencies. Clinics are usually staffed with orthopedists. However, many of these children, especially those with cerebral palsy, need other specialists' services for their proper training.

"The procedure of securing correction of physical handicaps by the 'children's court procedure' is unwieldy and outmoded and we recommend a simplified method which operates through medical and not legal authority. Greater efforts should be made to provide these specialized services for those handicapped children who would profit by them. Services for handicapped children, not only those with orthopedic conditions, but also for those with heart disease, hearing and vision defects, cancer, etc., should be coordinated with general pediatric services in order to provide not only more complete health supervision of children but to avoid duplication and overlapping of service through special programs.

"Other important problems, inadequately touched upon because of the limitations of the data, but which demand pediatric study and leadership nevertheless are accidents in childhood, by far the leading cause of death in children from 1 to 15; rheumatic fever and heart disease which is a major disease problem beginning at the school ages; and cancer which has been emerging in recent years as a prime cause of mortality in children because of better diagnosis and the decrease in deaths due to other causes.

"This is a big program, but it is not an impossible one. Our State has a fine tradition of leadership in the field of child health. The Study shows that even at the present time we rank well above the national average in providing care for our children. But *all* our children deserve the full benefits of modern medical care. We feel confident that this challenge will be met."

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PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

A GREATER proportion of births in the United States were delivered in hospitals or institutions in 1947 than in any previous year on record. The number of registered live births rose to a peak of 3,699,940 in 1947, according to a report by Surgeon General Leonard A. Scheele of the Public Health Service. At the same time the proportion occurring in hospitals reached a new high of 84.8%. An additional 10.1% of births in 1947 were attended by physicians outside of hospitals and only about 1 out of 20 births were delivered by a mid-wife or other nonphysician.

Since 1935, the first year that data of this kind became available, the percentage of total births delivered in hospitals has more than doubled, rising from 36.9% in 1935 to 84.8% in 1947, according to the report. This increase has been accompanied by a reduction in the proportion of live births delivered by physicians outside of hospitals, from 50.6 in 1935 to 10.1% in 1947, as well as a decline in the percentage delivered by nonphysicians, from 12.5 in 1935 to 5.1% in 1947.

The report shows significant progress in recent years in the use of medical and hospital facilities by both the white and nonwhite groups, and by both the urban and rural

TABLE I

PERCENTAGE DISTRIBUTION OF LIVE BIRTHS BY PERSON IN ATTENDANCE: UNITED STATES, 1940 AND 1947

A. Race

Person in Attendance	White		Nonwhite	
	1947	1940	1947	1940
Total	100.0	100.0	100.0	100.0
Physician in hospital*	89.3	59.9	49.7	26.7
Physician (not in hospital)	9.2	36.5	17.7	24.1
Midwife, other, and not specified	1.5	3.6	32.6	49.2

B. Urban and Rural Residence

Person in Attendance	Urban		Rural	
	1947	1940	1947	1940
Total	100.0	100.0	100.0	100.0
Physician (in hospital)*	93.8	76.0	71.3	32.3
Physician (not in hospital)	4.2	20.9	19.0	51.3
Midwife, other, and not specified	2.0	3.1	9.7	16.4

* It is assumed that all births in hospitals or institutions are attended by physicians.

population (see Table I). Considerable differences exist between these groups in the extent to which hospitals are used for confinements. In 1947, almost 9 in 10 of the white births occurred in hospitals as compared with about 1 in 2 of the nonwhite births. Only 1.5% of white births were attended by nonphysicians, but almost a third of the nonwhite births were delivered by midwives or other nonphysicians. The differences were less marked as between residents of urban and rural areas (see Table I).

In 1947, there were 11 states in which 10% or more of the births were attended by nonphysicians and 12 states in which 25% or more of the births occurred outside a hospital (see Table II).

TABLE II

PERCENTAGE DISTRIBUTION OF LIVE BIRTHS BY PERSON IN ATTENDANCE: UNITED STATES AND EACH STATE, 1947
(By place of residence)

Area	Total	Per cent attended by—		
		Physician (in hospital) *	Physician (not in hospital)	Midwife, other, and not specified
UNITED STATES	100.0	84.8	10.1	5.1
Alabama	100.0	54.3	24.3	21.5
Arizona	100.0	88.6	5.9	5.5
Arkansas	100.0	57.4	26.7	15.9
California	100.0	97.7	1.8	0.5
Colorado	100.0	90.6	8.6	0.8
Connecticut	100.0	99.3	0.7	0.0
Delaware	100.0	89.9	4.6	5.5
Dist. of Columbia	100.0	96.8	3.2	0.1
Florida	100.0	75.5	9.6	14.9
Georgia	100.0	64.4	13.9	21.6
Idaho	100.0	97.6	2.1	0.3
Illinois	100.0	94.5	5.3	0.3
Indiana	100.0	90.1	9.2	0.7
Iowa	100.0	94.3	5.6	0.1
Kansas	100.0	92.8	7.0	0.3
Kentucky	100.0	55.5	37.3	7.2
Louisiana	100.0	74.9	9.0	16.1
Maine	100.0	89.4	10.3	0.3
Maryland	100.0	81.9	13.8	4.3
Massachusetts	100.0	97.8	2.1	0.0
Michigan	100.0	95.3	4.5	0.2
Minnesota	100.0	96.5	3.3	0.2
Mississippi	100.0	41.9	19.5	38.6
Missouri	100.0	80.7	17.5	1.7
Montana	100.0	97.5	1.9	0.6
Nebraska	100.0	93.5	6.5	0.0
Nevada	100.0	97.8	1.8	0.4
New Hampshire	100.0	97.9	2.1	0.0
New Jersey	100.0	96.2	3.3	0.5
New Mexico	100.0	63.9	19.6	16.5
New York	100.0	97.5	2.3	0.2
North Carolina	100.0	65.6	22.1	12.2
North Dakota	100.0	92.9	6.3	0.8
Ohio	100.0	92.9	6.9	0.2
Oklahoma	100.0	80.6	16.4	3.0
Oregon	100.0	98.7	1.0	0.3
Pennsylvania	100.0	90.2	9.7	0.1
Rhode Island	100.0	97.7	2.0	0.3
South Carolina	100.0	52.5	19.0	28.5
South Dakota	100.0	89.4	9.6	1.0
Tennessee	100.0	66.0	26.7	7.4
Texas	100.0	75.2	13.5	11.3
Utah	100.0	97.6	2.2	0.1
Vermont	100.0	90.3	9.6	0.0
Virginia	100.0	67.8	19.8	12.3
Washington	100.0	98.7	1.1	0.1
West Virginia	100.0	59.1	38.5	2.4
Wisconsin	100.0	95.5	4.3	0.2
Wyoming	100.0	94.8	4.8	0.4

* It is assumed that all births in hospitals or institutions are attended by physicians.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

CHILD HEALTH IN GREAT BRITAIN

A report* published for the Socialist Medical Association of Great Britain regards reductions in mortality in the last 50 years as mainly due to improved living standards, the first fruits of a social revolution. For major causes of death and disability, however, there are still class differences of over 100% due to environmental and therefore removable handicaps. Improved medical services are important, but secondary. Since children now form only 20% of the population, economic necessity as well as social justice demand that protection and encouragement of child health should become an absolute priority in national service. New legislation (education, insurance, health) provides a framework in which rapid exploitation of 20th century science is possible, and the report is emphatic that it is the positive and preventive obligations of child health service which are of primary importance. Remedial services still require large developments, but preoccupation with them must not obscure the fact that the need for doctors, nurses and hospitals can be steadily reduced by good nurture.

The first needs, therefore, are good food, houses and schools, physical culture and the happy employment of leisure. Class differences in stature and physique can be abolished by food supplements to primary school children: food rationing, food subsidies and free school meals have prevented deterioration in child health during the economic stress of war and postwar years. The report urges more rapid provision for meals for all school children, better family endowment, state control of milk production and distribution and increase rather than reduction of food subsidies. Better training of doctors and nurses in lactation would increase the number of women who can nurse their infants. Physical training in secondary schools is given by gymnasts, but not in primary schools where it is of even greater importance: development of physique is only second to good food in protecting against disease. Organized games, holiday camps and good play centers in cities are required; more children of poor physique should go to residential open-air schools.

Opportunity for research into the methods of health service itself and the technics of education in bodily and mental hygiene is provided by the reorganization of administration into larger units, and should be a responsibility not only of university centers but also of county health departments and regional hospital boards. The report is critical of the fact that administrative responsibility for developing child health service remains divided between several ministries, regional and county authorities. Advisory committees composed largely of health workers (doctors, nurses, social workers) are required at all levels of organization: service for children demands good team work. The large administrative organization is dangerous unless provision is made for effective semi-autonomous units in which parents, teachers and health workers can contribute to policy.

School services especially need reform, both in the content of their programmes and in order to give increased opportunity for individual initiative to staff. Organization of teams consisting of full-time health officers, family doctors, health visitors and social workers are recommended, to serve child populations of 2500 to 5000, from birth to adolescence; each team should be based on a health center. The needs of child health service demand a new and more carefully devised scheme of training for health workers, including doctors, whose economic and professional status is overdue for reform.

Remedial medicine must not be divorced from positive health service. In each medical specialty and within each administrative region, a programme of work and organization is needed, and should be worked out largely through advisory committees so that the needs of preventive medicine are

* Child Health: Survey and Proposals, published for the Socialist Medical Association, London, Today and Tomorrow Publications, Ltd., 1949.

brought constantly to the notice of medical specialists. Greater use should be made of technical assistants in ophthalmology, dentistry, orthopedics and otorhinology, and in the teaching of hygiene; the essentials are suggested for a programme of work in each field. Pediatric hospital service, apart from university centers, is still largely undeveloped; pediatric departments should form part of large general hospitals, undertake postgraduate teaching and provide essential contacts between hospitals, family doctors and child health staff. Home consultation should diminish the need for hospital admissions.

Tuberculosis, it is maintained, could be eradicated in a few years if the need were regarded as urgent and the country's conscience not lulled by statistical evidence to show that tuberculosis is "controlled." Over 3000 children die of it annually and the seeds of adult tuberculosis are sown in many thousands more, themselves to infect the next generation. The reforms advocated are (a) concentration on the provision of hospital beds for all "open" cases, with strict enforcement of notification; (b) nationalization of the milk industry; (c) tuberculin testing of all children; (d) exploitation of BCG vaccine for all children known to be at risk.

Services for disabled, mentally defective and maladjusted children are also considered in the report, which ends by summarizing the conclusions of the committee of doctors, nurses, dentists, opticians, etc., appointed by the Association, in the form of 32 recommendations.

DUNCAN G. LEYS, M.D.

UNIVERSITY OF LIVERPOOL: DEPARTMENT OF CHILD HEALTH

A lectureship in diseases of infants and children was established in 1882 at University College, Liverpool (subsequently the University of Liverpool) but it was not until 1944 that the University Department of Child Health was opened under the direction of the Professor of Child Health. This development was made possible by collaboration between the University, the City Council (representing prophylactic paediatrics and in control of Alder Hey Children's Hospital) and the Royal Liverpool Children's Hospital ("voluntary" hospital), and the scheme was designed to promote further cooperation between these various interests for the study of preventive and curative paediatrics, and for more comprehensive teaching and research. The fundamental changes in hospital management which took place on July 5, 1948, when the National Health Service came into operation, have not interfered with the basic idea of the scheme, and in the Department of Child Health the University is now linked with the City Council (for prophylactic paediatrics), with the Liverpool Regional Hospital Board (Alder Hey Children's Hospital and the neonatal unit at Mill Road Hospital), and with the Board of Governors (Royal Liverpool Children's Hospital and the neonatal unit of the Liverpool Maternity Hospital).

The staff of the Department consists of the Professor of Child Health, the First and Second Assistants, a Senior Lecturer and a Lecturer in Child Health (both full time), four Lecturers and Assistant Lectures in Clinical Paediatrics, two Lecturers in Clinical (Preventive) Paediatrics, two secretaries, together with Medical Registrars, etc.

The administrative offices of the Department are at Alder Hey Children's Hospital and include two lecture theatres, two research laboratories, library, pathologic museum and photographic room, in addition to the necessary rooms for the use of members of the staff and two secretaries. The professorial clinical unit at Alder Hey Hospital consists of two wards each containing 14 single cubicles (chiefly for infants) and two wards (one male and one female) each of 30 beds, for children up to the age of 15 years. The hospital is a large general hospital for children, admitting about 7,000 patients annually, and all are available for teaching purposes. They include a full range of medical, general surgical, orthopaedic and "special" paediatric cases (such as ear, nose and throat, ophthalmic, plastic surgery and primary tuberculosis).

At the City Branch of the Royal Liverpool Children's Hospital—also a general hospital for children—there are 68 surgical and 68 medical beds (28 under the charge of the Professor). At the Heswall Branch (of which Sir Robert Jones and Dr. Charles Macalister were the chief founders; it is situated in the country about 10 miles from Liverpool and provides good facilities for open-air treatment) 250 beds are available—mainly for long-stay medical, surgical and orthopaedic cases. The Royal Liverpool Children's Hospital admits about 2,500 patients per year and has a large outpatient department, where 23,000 new cases were seen during 1948. Liverpool Maternity Hospital and Mill Road Hospital provide facilities for neonatal paediatrics; each has 100 obstetric beds in use and 2,500 deliveries annually and at Mill Road there is a premature baby unit of 12 cots.

Tuition to Medical Students

The teaching of undergraduate medical students takes place mainly at the Royal Liverpool Children's Hospital, which is situated conveniently near to the University Medical School.

Between 70 and 80 students are given instruction in clinical paediatrics each year; the teaching is given both by the professorial team and by the nonprofessorial teaching staff. Approximately 10 students are allocated to each "clinical unit" and receive instruction for one month from the professorial "unit" and one month from the nonprofessorial "unit." During this two month period approximately 76 hours are spent in the hospital wards and 58 hours in the outpatient departments, including child welfare clinics and school clinics. It has not been possible, so far, to arrange for students to have a period of residence in hospital. Fifteen academic lectures in paediatrics are given during the year and in addition eight clinical lectures are attended by each student during his two-monthly period of clinical paediatrics. Instruction in neonatal paediatrics is given to students during their (residential) period of clinical obstetrics at the Liverpool Maternity Hospital and Mill Road Hospital.

In the final M.B. examination there is no separate paper in Child Health but two of the 10 compulsory questions in medicine are on paediatric subjects and the clinical examination includes paediatrics cases.

Tuition to Postgraduate

This is given chiefly at Alder Hey Children's Hospital and includes:

1. A ward round, followed by a lecture, one morning each week throughout the year at Alder Hey Children's Hospital. This class is attended by postgraduates studying for higher degrees or diplomas (M.R.C.P. and D.C.H.), school medical officers and child welfare officers.

2. Full time three week refresher courses in paediatrics held twice yearly. These are intended primarily for doctors in the area of the Liverpool Regional Hospital Board who are engaged in preventive and curative paediatrics, but other applicants are accepted up to a total number of 20 per course. The Ministries of Health and Education have recognized these courses for "grant" purposes.

3. Courses for general practitioners in the area from time to time.

4. A teaching round once weekly at the Liverpool Maternity Hospital at which problems of neonatal paediatrics are discussed and clinical cases are demonstrated.

5. Tuition to a small number of postgraduates, mostly from overseas, who work in the Department for periods of 3 to 12 months.

For the degree of M.D. (Liverpool) a candidate may elect to take Child Health as a special subject.

Courses of instruction in child care, etc., are given by members of the Department to school teachers, foster mothers and other workers in the fields of paediatrics and social medicine, and a course of 24 lectures is given each year to students taking the University Diploma in Child Care.

Research

The Department was one of the original centres selected by the Medical Research Council for the clinical trials of streptomycin in tuberculosis; this work continues and has been enlarged to include a wider study of tuberculosis in infancy. A study, also on behalf of the Medical Research Council, was concerned with the chemoprophylaxis of childhood rheumatism, and a survey of ward infection has been carried out on behalf of the British Paediatric Association. A full time research worker, appointed by the Medical Research Council, is at present studying infections in infancy, with special reference to diarrhoea and vomiting. Three "Cow and Gate" scholars have worked in the Department during the past year and have studied breastfeeding, rheumatic infection in childhood and congenital disorders of the urinary tract. Another of these scholars has begun work upon convalescence in childhood.

NORMAN B. CAPON, M.D.

NEWS AND ANNOUNCEMENTS

The gift of a $10,000 Subsidiary Scholarship to the Chicago Medical School in memory of the late Dr. I. Harrison Tumpeer is announced by Dr. John J. Sheinin, dean of the school.

For a period of two years, Dr. Tumpeer was an associate of Dr. Isaac A. Abt, and then was appointed to the staff of Michael Reese Hospital and the Post Graduate Medical Staff and Hospital. Of the latter, he became Professor and head of the Pediatric Department. He was also Adjunct Pediatrician of the Michael Reese Hospital, Director of the Pediatric Department of the Michael Reese Dispensary and Attending Pediatrician. He was credited for the rapid development of the medical library at Michael Reese, one of the largest not associated with any medical school.

Dr. I. Harrison Tumpeer Subsidiary Scholarship is among the first received under a new subsidiary scholarship plan created by The Chicago Medical School in order to subsidize the complete education of a medical student for a period of four years. The subsidiary scholarships as established by The Chicago Medical School represent the difference between what the student pays in tuition during his four years and the amount of money the college has to expend during the same four years in order to maintain the high quality of training required by accredited medical institutions.

* * *

Continuation Courses in Pediatric Roentgenology

The University of Minnesota announces a continuation course in Pediatric Roentgenology on Oct. 31 through Nov. 5, 1949. The course, which will be presented at the Center for Continuation Study, is intended for radiologists and pediatricians. The material to be presented will include the basic medical sciences, clinical medicine and diagnostic roentgenology, as it pertains to general and special problems in the field of childhood diseases. Presentation will be by means of lectures, clinics, conferences and round table discussions.

Visiting physicians who will participate as members of the faculty for the course will include Dr. John Caffey, Babies Hospital, Columbia University Medical Center; Dr. Edward B. D. Neuhauser, Children's Hospital, Boston; Dr. Edith Potter, University of Chicago, and Dr. Frederic N. Silverman, Children's Hospital, Cincinnati. The remainder of the faculty for the course will be made up of clinical and full-time members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

* * *

Postgraduate Course: Problems of Newborn Infants, Premature and Full Term

A postgraduate course on the Problems of Newborn Infants, Premature and Full Term, sponsored by the University of Colorado School of Medicine and the Colorado State Department of Health, will be given at the University of Colorado Medical Center, Denver, Colo., Nov. 2, 3, 4 and 5, 1949. The course is for the purpose of orienting the practicing physicians in the problems of newborn infants, both premature and full term.

Inquiries should be directed to the Director, Graduate and Postgraduate Medical Education, University of Colorado School of Medicine, Denver, Colo.

* * *

Postgraduate Course: Poliomyelitis for Physicians

Aided by a grant from the National Foundation for Infantile Paralysis, the University of Colorado Medical Center is continuing to offer to physicians a series of postgraduate courses on poliomyelitis. Emphasis will be placed upon the comprehensive care of patients in an epidemic.

The courses are open to physicians who reside in states west of the Mississippi. Three one week courses are scheduled: Nov. 7-11, incl., March 13-18, incl., and May 22-27, incl., 1950.

For further information, address correspondence to Director of Poliomyelitis Teaching Program, University of Colorado Medical Center, Denver, Colo.

* * *

Dr. Alex J. Steigman is serving as Consultant in Clinical Epidemiology for The National Foundation for Infantile Paralysis, Inc. Dr. Steigman's temporary departure from pediatrics will be for

the purpose of field work in early diagnosis, management and epidemiologic investigations of poliomyelitis. He has been associated with the pediatric departments at the Universities of Pennsylvania, Harvard and Temple. Dr. Steigman has been Senior Fellow in Pediatrics, National Research Council, at the Children's Hospital Research Foundation in Cincinnati.

* * *

The appointment of Dr. Lester J. Evans, medical associate of the Commonwealth Fund, as consultant in medical education to the State University of New York has been announced.

He will assume his duties with the state university immediately. He also plans to continue on a part-time basis his duties with the Commonwealth Fund, with which he has been associated since 1923.

* * *

Promotion of Dr. Robert Ward from Associate Professor to full Professor of Pediatrics at New York University's College of Medicine has been announced.

* * *

The following changes have been made in State Chairmen of the American Academy of Pediatrics: Dr. William W. Belford, San Diego, succeeds Dr. Russell W. Mapes as Co-Chairman for the State of California; Dr. Paul E. Belknap, Topeka, succeeds Dr. Bertrand I. Krehbiel as Chairman for the State of Kansas.

* * *

Arrangements are being made for special train travel service to the Annual Meeting of the Academy of Pediatrics in San Francisco in November. The United States Travel Agency will conduct a special train leaving Chicago on November 7. Information may be obtained from the Agency, 807 15th Street N.W., Washington 5, D.C.

* * *

Copies of "Recommended Practices for the Control of Poliomyelitis," formulated by the National Conference on Recommended Practices for the Control of Poliomyelitis, which was held in Ann Arbor, Mich., June 1949, and sponsored by The National Foundation for Infantile Paralysis, Inc., are available on request from The National Foundation for Infantile Paralysis, Inc., 120 Broadway, New York 5, N.Y.

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Transactions of the Fifth International Congress on Pediatrics are available on order from: Almquist & Wiksells, Boktryckeri Aktiebolag, Huvudkontoret, Uppsala, Sweden. The price is 25 Swedish crowns.

BOOK REVIEWS

PEDIATRIC ANESTHESIA, M. Digby Leigh, M.D., and M. Kathleen Beltom, M.D., New York, The MacMillan Company, 1948, $5.50, 232 pp.

For those who are interested in the advancement of pediatric surgery, it has long been obvious that improvements should be made in anesthesia for infants and children. Much credit should go to Drs. Leigh and Beltom for their important efforts in this direction. The present volume is based on an extensive experience with anesthesia technics in young subjects and hence bears a mark of authority. The book is a good source of reference data for those who are called upon to work in this field. Preoperative evaluation of patients and discussion of premedication are well presented, as are the subjects of postoperative support, fluid therapy and transfusion. A wide variety of anesthesia technics are admirably described. The authors have stressed the important fact that a quiet, cheerful and relaxing approach to a child in the immediate pre-anesthetic period may be fully as important as the proper selection and administration of drugs.

There is a long and important chapter on the choice of anesthetic agents and technics for various types of surgical procedures, discussing points of especial interest in each of these surgical endeavors and indicating the anesthetist's point of view of each of these situations.

The book contains little in the way of discussion of physiologic backgrounds of anesthesia, an approach which probably increases its value to those general anesthetists or physicians who want to use it as a practical guide for their anesthetic problems in infants and children. Exceedingly complicated anesthetic combinations or procedures have for the most part been omitted and the reader is not left with a false impression that cumbersome and highly specialized technics are necessary for success in this field.

One wonders whether it would not have been better to omit the suggestion that artificial production of a pneumothorax for 3 or 4 days before a surgical attack on a patent ductus arteriosus be done. Furthermore, it seems superfluous and possibly dangerous to suggest that intratracheal intubation, nitrous oxide-oxygen anesthesia and curare are acceptable for pyloromyotomy operations.

The authors are to be congratulated in taking a firm stand against the theory that deaths occur from "status lymphaticus." They rightfully point to the conclusion that "thymic death" is usually a figment of the imagination and the term actually covers up an anesthetic or surgical sin.

This small volume fills a long-felt need and certainly should be in the hands of all physicians or nurse anesthetists who are called upon to anesthetize babies and small children.

OBESITY, Edward H. Rynearson, M.D., and Clifford F. Gastineau, M.D., American Lecture Series, No. 36, Springfield, Ill., Charles C Thomas, Publisher, 1949, $3.50, 144 pp., 9 figures, 16 tables.

This monograph of 100 odd text pages merits being characterized as both comprehensive and critical on the one hand and concise and constructive on the other. While in the main, the discussion relates to adults, obesity in children is not neglected and the attitude of the authors reflects the most widely accepted pediatric thinking on the matter.

The introduction points out the hazard to health and longevity which obesity carries. With respect to physiology, it is emphasized that no abnormality which violates the principles of the conservation of energy has ever been demonstrated. The discussion of etiology is thorough and well balanced, appropriate attention being given to neurologic, emotional, endocrine, hereditary, environmental and other factors. Contraindications to reduction of weight are dealt with briefly. Convinced that restriction of intake of food is the only effective therapeutic approach, a detailed description of the technic of dieting is supplied under the authorship of Alice Karslake Irmisch, dietician at the Mayo Clinic. The importance of psychologic factors is stressed. Supplementary drug therapy is discussed and some of the sympathicomimetic amines are given qualified approval. Harmful and ineffective methods are accorded appropriate attention. The bibliography lists 422 references.

This volume can be recommended as a source of authoritative information to any physician who

has not had the opportunity through experience or wide reading to develop an objective and effective point of view toward a common and often harassing problem.

MODERN TRENDS IN PUBLIC HEALTH, edited by Arthur Massey, C.B.E., M.D., D.P.H., D.P.A., New York, Paul B. Hoeber, Inc., London, Butterworth & Co., Ltd., 1949, $12.50, 581 pp.

During World War II rapid advances in the field of public health have been made so that a book on "modern trends" is certain to be of great value to those who wish to be brought up to date. The subjects selected vary from the social aspects of home and family life, nutrition, housing, child health, rheumatism, tuberculosis, occupational health; the relationship of public health to laboratory and academic medicine, to dentistry and to mental health; pollution of the atmosphere; vital statistics and also the various aspects of health education. Dr. Massey has selected his subjects from a wide field and the contributors, as specialists, have each done credit to their subject so that the book makes excellent reading, informative and interesting.

Several authors refer to the importance of centralizing health and social problems around the family doctor. Dr. W. Edwards believes that a better liaison between the general practitioner and specialist would be of more value than special postgraduate courses for the practitioner. He also believes preventive pediatrics should be in the hands of the general practitioner. Dr. J. J. Jervis reveals the startling fact that owing to pollution of the atmosphere there is a 70% reduction of ultra violet light rays in Leeds; furthermore, he shows a direct relationship between deaths from respiratory disease and the quantity of soot in the atmosphere. Dr. Percy Stocks reviews the Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, to be issued by the World Health Organisation in 1949 or 1950. Finally, Dr. Robert Sutherland shows the important part the doctor plays in health education and he suggests that each major authority should appoint a health education officer. This book is not just for public health students but should be read by all who wish to keep in touch with modern thought and progress.

HELP THEM HELP THEMSELVES, Juliette McIntosh Gratke, Dallas, Texas, The Texas Society for Crippled Children, 1947, $2.50, 184 pp.

The author of this book is adequately equipped to discuss the problem of the cerebral palsied child from the viewpoint of both the therapist and the parent. Not only has she been actively engaged in her professional capacity as a speech pathologist in the treatment of these children, but she is also the mother of a child so afflicted.

The author introduces the subject by describing the problem that she had to face as a mother. She then proceeds to discuss the general training problem in these children including the feeding, sleeping, toilet training, training for locomotion, hand function, speech and general education of the child.

The most authoritative section deals with speech training in which the author is well qualified. Rhymes, songs and specific physiotherapy instruction for the parents are included. The book is illustrated with photographs which have suffered in reproduction and printing.

The book is well written with a warmth in style and personal touch which gives it a sincere and charming quality. It is one of the best such books written by either a parent or a training technician and is to be highly recommended for both parents and therapists working with such children.

OBSERVATIONS ON THE PATHOLOGY OF HYDROCEPHALUS, Dorothy S. Russell, London, His Majesty's Stationery Office, 1949, 6s, 135 pp., 90 illustrations.

Professor Russell's superb monograph takes as its point of view that "the common background of hydrocephalus is formed by the single factor of obstruction, and the immense variety of pathological lesions productive of hydrocephalus have this single feature in common: all create an obstruction at some point in the pathway of the cerebrospinal fluid." In each instance of a large series of cases, Russell has been able to identify the cause of the obstruction, a record hardly approached in most neuropathologic laboratories.

The results are discussed on an etiologic basis. Of the malformations, particular emphasis is given to stenosis and forking of the aqueduct and the Arnold-Chiari malformation. Abundant evidence

is presented that hydrocephalus associated with meningocele is not due to traction resulting from fixation of the spinal cord at the meningocele site. A chapter is devoted to a form of progressive gliosis of the aqueduct leading to gradually increasing hydrocephalus. The condition is of uncertain etiology, though Russell presents some evidence that it may be the result of inflammation. The frankly inflammatory lesions are treated thoroughly. Russell has gathered evidence that certain instances of hydrocephalus are due to clinically unrecognized meningeal inflammation a long time previously. Dural sinus thrombosis with survival is regarded as a cause of mild or moderate hydrocephalus, perhaps reversible in part. Neoplasms as a cause of hydrocephalus are discussed briefly but adequately. There is an especially valuable chapter on the anatomic effects of hydrocephalus *per se*.

The distinction of this monograph depends in part on the meticulous study of a large material; on fair and dispassionate presentation of all points of view; on the breadth of understanding which unites neuropathologic investigation with relevant clinical and experimental data, and on the distinguished literary style. The illustrations are well chosen and clearly reproduced. The paper and printing are satisfactory, but so valuable a monograph would seem to merit a more secure binding.

This book is by far the best available discussion of hydrocephalus. It is indispensable to anyone concerned with this condition, whether neuropathologist, neurosurgeon, pediatrician or roentgenologist. The reviewer would like to point out also that those interested in the best methods for presenting scientific material could have no better model than this monograph.

Diagnostic Tests for Infants and Children, H. Behrendt, M.D., New York and London, Interscience Publishers, Inc., 1949, $7.50, 529 pp.

This is a timely guide on diagnostic methods which will be especially useful to pediatricians, medical students and laboratory technicians who do not have ready access to large medical libraries. Physicians generally know too little regarding the methods employed in providing the data upon which their daily work is based. In the main this lack of familiarity with the principles underlying special tests and procedures can be attributed to the difficulty of obtaining simple explanatory outlines of the methods which are referred to in the briefest manner possible in current journals and textbooks.

Available handbooks on laboratory procedures, like the clinical laboratories in most of our general hospitals, are designed almost exclusively with the adult patient in mind, little attention being given to the special conditions required for application of tests in infants and young children. This new book goes a long way toward making up for the obvious deficiency in such standard manuals. The intellectually curious reader will be grateful for the author's emphasis on underlying principles and interpretations, as well as on the special adaptations of all procedures for pediatric use.

The major portion of the book is devoted to special diagnostic tests designed to evaluate the functional status of organs and systems in a quantitative manner. In addition there are chapters dealing with methods for such broad subjects as carbohydrate, protein, fat and energy metabolism, electrolyte and water exchanges and vitamin nutrition tests. The chapter on immunologic methods deals satisfactorily with hypersensitivity tests and blood groups and the Rh factor. In the chapter on inorganic body constituents, calcium and phosphorus are dealt with extensively, while the reader is referred to other literature for the methods for determination of potassium which is currently of such great interest to pediatricians. Perhaps this imbalance in emphasis is due to the fact that the author was able to cover the literature up to 1946 only. Other useful tests in other categories have probably been omitted for the same reason. Little reference is made to bacteriologic and biologic methods, perhaps because their use requires no special adaptation or interpretation for pediatric patients.

A unique feature of the book is its consideration of neurophysiologic and psychologic test technics, including tests for hearing and sight. Altogether the book is a useful one which pediatricians will welcome.

Speech Handicapped School Children, Wendell Johnson, Spencer F. Brown, Clarence W. Edney, James F. Curtis and Jacqueline Keaster, New York, Harper & Brothers, 1948, $3.00, 464 pp.

The authors have stated that this book is first of all a text on speech disorders and correction written primarily for students preparing to teach. They are to be congratulated on so successfully accomplishing their aim. The text is the right length, the essentials of the subject completely and

clearly presented in understandable terms for anyone even remotely interested in the subject. For all persons supervising or teaching our American children it should be a "must own" book. The authors patently have spent much time and thought in compiling the contents and it is evident they are thoroughly acquainted with the subject. Their enthusiasm in their sincere humanitarian plea to the school teacher to mold and develop the pupil's mind and personality is admirable.

They state that 5 to 10% of school children have speech defects. The book deals with phonetics, the normal voice, disorders of voice, articulation, stuttering, retarded speech, speech problems associated with cleft palate and cerebral palsy, and hearing difficulties. Fundamentally the book deals with three major questions: 1. What kinds of speech defects are found among school children? 2. What can the classroom school teachers do about them on her own or in cooperation with a speech correctionist? 3. What would the classroom teacher be advised to avoid doing to, for or about children with speech defects?

Although the book is a text book of most valuable instruction to the classroom teacher, it should be read by the teacher in training, the school administrator, the school nurse, the social worker, the psychologist, the dentist, the school physician, the pediatrician, the speech correctionist and the interested parent. As the book states, each is dedicated to the task of teaching the American child and each is determined that in the program of education for all the speech handicapped child must be neither neglected nor ignored.

WEBSTER'S NEW COLLEGIATE DICTIONARY, Springfield, Mass., G. & C. Merriam and Company, 1949, pp. xxii + 1209.

This is a new edition, with an addition of "new," to the title of the Vth edition of Webster's Collegiate Dictionary. Both editions are based on Webster's New International Dictionary, edition II. Material of the previous edition has been retained but many new terms and meanings, older terms and meanings of increasing importance or frequency and abbreviations and proper names have been added by using a wider page and a wider column. Previous editions showed pages xxxiv + 1274, each page size being 8 x 4 3/4 inches, the present edition having page size of 8 11/16 x 5 3/4 inches. The type face is the same as the New International Edition II.

The section on introductory matter makes up pages vii to xxii, the dictionary pages 1 to 997 and the several appendices pages 998 to 1209.

The most interesting feature of this new edition is to scan through the pages noting the new words that have been given permanent place in such a record of the formation and development of the American style of language. It is easy in comparing the two previous editions to recognize the steady progress of language growth. Language and words are living things and go forward with other customs and forms of progress. Mencken's history *The American Language* makes an interesting companion piece when one "reads the dictionary."

Special mention should be made of medical and other scientific words which are included. One is surprised to note the accuracy of definitions givens in terms which are easily understood by the layman as well as the professional reader; for example, thrombokinase, on page 886, "a substance present in the tissues which accelerates the clotting of blood." The physician, therefore, will find this useful as a medical dictionary.

NEW AND NONOFFICIAL REMEDIES, Philadelphia, J. B. Lippincott Company, 1949, $3.00, 805 pp.

This book is issued annually under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. It contains the descriptions of articles which the Council has found acceptable up to June 15 of the year of publication. The descriptions are based in part on investigations made by or under the direction of the Council and in part on evidence or information supplied by the manufacturer or his agent.

The book contains the official rules of the Council together with various procedures set up by the Council: 1. Form for presentation of articles for NNR. 2. Criteria for evaluation of certain products. 3. Decisions of general interest. This edition follows the usual form of presentation. The first section describes in 24 chapters of 572 pages the general remedies and preparations included. The second section gives tests and standards and the index is in the third section. This is an essential must reference book.

Pediatrics

VOLUME 4 OCTOBER 1949 NUMBER 4

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

DIVISION III

REPORT OF THE MEETING OF THE EXECUTIVE BOARD

A meeting of the Executive Board of the American Academy of Pediatrics was held at the Palmer House, Chicago, Ill., June 24, 25 and 26, 1949. The Friday morning session was called to order at 10:15 a.m. by the President, Dr. Warren R. Sisson.

The following were present: Drs. Sisson, Shaw, Stringfield, Beaven, Barba, Hoyer, Pease, Bost, McElhenney, Munns, Grulee and Martmer.

The following applicants for fellowship were elected:

District I: Leo B. Burgin, Brookline, Mass.; Francis W. Helfrick, Manchester, Conn.; Allen Malcolm Hill, S. Hamilton, Mass.; Alice Chassel Nauen, Cambridge, Mass.; Pauline Owyang, Boston; Maurice Ross, Saco, Me.; Isaac Hillson Schwartz, New Bedford, Mass.

District II: Grace A. Altenau, Brooklyn; John Mitchell Brush, New York; Samuel Brusilow, Brooklyn; Harold S. Cole, New York; Carl Drayer, Brooklyn; Alla Dunewitz, Brooklyn; William C. Friedman, Far Rockaway, L.I., N.Y.; Saul Krugman, New York; William I. Levinstein, Rochester, N.Y.; Nina R. Lief, Far Rockaway, L.I., N.Y.; Sidney S. Marder, St. Albans, N.Y.; Frederick N. Roberts, Syracuse, N.Y.; George David Rook, New York; Jonas S. Rosenberg, Batavia, N.Y.; Estelle Siker, Port Chester, N.Y.; Vincent A. Spinelli, Yonkers, N.Y.; Norbert Paul Sullivan, Jackson Heights, L.I., N.Y.; Leo M. Taran, New York; Alex C. Zarchy, Far Rockaway, L.I., N.Y.

District III: Curtis A. Beerman, Westmont, Johnstown, Pa.; L. Clair Burket, Altoona, Pa.; Maclyn Cagan, North Arlington, N.J.; Howard Yeager Harris, Kingston, Pa.; Louis L. Krafchik, New Brunswick, N.J.; Bernard B. Lilien, Irvington, N.J.; W. Clair Merriman, Beaver, Pa.; Bernard C. Prietsch, Pittsburgh; Edward Hoge Vick, Narberth, Pa.; Milton Michael Willner, Newark; Armine Taylor Wilson, Wilmington; Dominic S. Motsay, Sayre, Pa.

District IV: Frederic Gerard Burke, Bethesda, Md.; C. Benton Burns, Columbia, S.C.; Elizabeth Conrad, Winston-Salem; James Taylor Cowart, Tampa; William Howell Kiser, Jr., Atlanta; Carolyn Moore McCue, Richmond; John D. McKey, Orlando, Fla.; Archibald Hanes Pate, Goldsboro, N.C.

District V: Frederick Merrill Adams, Birmingham, Mich.; Herbert I. Arbeiter, Hammond, Ind.; Eugene W. Austin, Evansville, Ind.; Harry F. Becker, Battle Creek, Mich.; Stephen C. Bradley, Terre Haute, Ind.; M. Armacost Cox, Toronto; Leonard T. Davidson, Crestwood, Ky.; Harold Edwin Edwards, Toronto; Ralph I. Fried, Cleveland; William W. Herman, Cleveland; H. Bryan Hutt, Youngstown, Ohio; Eugene Kaplan, Detroit; Elliott Podoll, Louisville; Mary Louise L. Scholl, Columbus; Jerome Earl Webber, Grand Rapids, Mich.; Richard Edward Wolf, Cincinnati.

District VI: Charles J. Baker, Fort Dodge, Iowa; James A. Conner, Chicago; Thomas V. Geppert, Madison, Wis.; Harry T. Nagel, Maywood, Ill.; Herbert F. Philipsborn, Jr., Glencoe, Ill.; Paul P.

Pierce, Alton, Ill.; Edward L. Strem, St. Paul, Minn.; John D. Stull, Olney, Ill.; Elsie Wieczorowski, Chicago.

District VII: Mathew D. Burnett, Jr., Houston; Edward Perry Crump, Nashville; Jackson Kazuo Eto, St. Louis; Caldwell K. Hamilton, Kirkwood, Mo.; George C. McCullough, Birmingham; Luther L. McDougal, Jr., Tupelo, Miss.; LeRoy Jules Stephens, St. Louis; C. O. Terrell, Jr., Fort Worth; Jerome A. Weaver, Birmingham; Erle Ewing Wilkinson, Nashville.

District VIII: Mason H. Abramson, Redwood City, Calif.; Albert T. Aldrich, Beverly Hills, Calif.; George Orion Boucher, Long Beach, Calif.; Robert Cohen, East Bakersfield, Calif.; Charles Louis Dimmler, Jr., Oakland; James Otis Dowrie, Sacramento; Anita E. Faverman, San Francisco; Robert L. Forney, Bakersfield, Calif.; Dan Campbell McDougall, Pocatello, Idaho; Jean Louis McMahon, Denver; Aaron Nisenson, Los Angeles; Edgar M. Rector, Portland; Francis H. Redewill, Jr., Whittier, Calif.; Melvin H. Schwartz, Oakland; Albert John Sheldon, Santa Ana, Calif.; Meritt William Stark, Denver.

District IX: Cecilio Abela, La Paz, Bolivia; Jaime Ramirez Acha, La Paz, Bolivia; Oscar Camacho Melean, La Paz, Bolivia; Carlos Daza Meruvia, La Paz, Bolivia; Carlos Ferrufino, La Paz, Bolivia; Armando Lopez Sanchez, La Paz, Bolivia; Julio Pereira, La Paz, Bolivia; Antonio Pizarro Gomez, La Paz, Bolivia; Luis V. Sotelo, La Paz, Bolivia; Francisco Torres Bracamonte, La Paz, Bolivia; Ernesto Trigo Pizarro, La Paz, Bolivia; Honoria Aguirre Armijo, Santiago de Chile, Chile; Rene Montero de la Pedraja, Vedado, Habaña, Cuba; Oscar Ortiz Machado, Camaguey, Cuba; Diego Sosa Bens, Almendares, Habana, Cuba; Julio Munoz Puglisevich, Lima, Peru.

Emeritus Fellowships were granted to the following: Charles E. Boynton, Ponte Vedra Beach, Fla.; George M. Lyon, Washington, D.C.; E. Kearney Smith, Lancaster, Pa.; Edward J. Wynkoop, Syracuse, N.Y.

Resignations of the following members were accepted: Cole B. Gibson, Meriden, Conn.; Hector Cantonnet, Montevideo, Uruguay; Rito Etchelar, Montevideo, Uruguay; Julio Lorenzo y Deal, Montevideo, Uruguay; Alejandro Volpe, Montevideo, Uruguay.

William S. Langford, New York, was elected to Associate Fellowship.

The following letter from Dr. Vernon W. Spickard, Seattle, was read and discussed:

"Before the next Board meeting I would like to submit a plan to take into the Academy as associate members a large number of practicing pediatricians who are doing good work for the children of the country but who may not have met the American Board of Pediatrics' requirements or who are unable to pass the Board.

"This group would pay full dues, but have no vote. I believe each applicant should have the unanimous approval of all the members in his state.

"There is a large group of these men active in local and regional pediatric societies, where associate membership would make enthusiastic supporters of the Academy, and we are going to need all the support we can get in the near future.

"A change in the By-laws covering associate membership would be necessary. Let me know what you think of the idea. I am sure Dr. Martmer and others are strongly in favor of the idea."

It was moved, seconded and carried that a committee of three be appointed by the President to take up this matter and report at the November meeting.

The afternoon session convened at 2 p.m., President Sisson presiding.

The Secretary's report was read as follows:

The Academy is about to enter upon its 20th year. In that time it has grown immensely in many respects. Not only has there been an increase in membership but the Academy has relatively increased in influence.

One of the latest advances has been to affiliate groups with the Academy who are interested in special phases of child care and therapy. The groups already organized are the groups in surgery and allergy. The group in mental health is being organized and will probably be ready to give us a definite proposition by the time of the meeting of the Academy in the Fall.

One of the principal activities that we have been engaged in during the last six months has been contacting the American Medical Association Board of Trustees so that their efforts and ours will be co-ordinated. I think we can say that due to the efforts of Drs. Oliver L. Stringfield, Warren R. Sisson and Philip S. Barba we have gone a long way towards accomplishing this end.

The dinner which was held in New York City to celebrate the conclusion of our Survey was one

example of this cooperation. This dinner was well set up but unfortunately we did not have as many guests as we had hoped to have.

A special meeting of the Executive Board was called by Dr. Sisson at Atlanta at the Areal Meeting for the purpose of discussing National Legislation and the appointment of a new reorganization committee.

The Survey Committee is about to hand in its final report at this meeting of the Executive Board and the ICH Committee must make new arrangements because of changed conditions.

The Committee on Cooperation with the American Legion with Dr. James G. Hughes as Chairman has been in active conference with the members of the American Legion assisted by Drs. John P. Hubbard and Glidden L. Brooks. We hope that something will come of this effort.

Pamphlets entitled, "Standards and Recommendations for Hospital Care of Newborn Infants—Full Term and Premature," brought out by the Committee on Fetus and Newborn have been selling well and the demand seems to be continuing. Apparently this will be a definite contribution in this field.

The Tumor Registry Committee has been very active and is continuing efforts to coordinate pathologic efforts throughout the country.

The journal, PEDIATRICS, under the able editorship of Dr. Hugh McCulloch and with the energetic efforts of Dr. Frank H. Lancaster as Chairman of the Publication Committee, is doing extremely well. I noticed in the last issue of PEDIATRICS we had 42 pages of advertising. The journal has already cleared up its past commitments to the Academy and, as near as can be told at the present time, has a definite net income.

The Second Pan-American Congress of Pediatrics will be held in Mexico City, November 2-5, 1949, at the Hotel del Prado. Our Mexican colleagues are making efforts to make this an outstanding affair and I am sure they will succeed. It is to be hoped that many of our members from the States will go there.

In addition to the San Francisco meeting, there will be an Areal Meeting at Philadelphia in the spring of 1950, and, in the fall, an Annual Meeting at Chicago. We are now working on the 1951 meeting which is projected to be held in Toronto. Hotel accommodations there may force us to change that location to some other place, possibly Montreal.

It is now my unhappy duty to report to you the deaths of the following members: George L. Cook, Tampa; Abraham M. Litvak, Brooklyn; John D. Lyttle, Los Angeles; Martin G. Neely, Birmingham; Worth Ross, Hartford; Eugene Rush, Philadelphia; M. Scherzer, Montreal; Lillian R. Smith, Hardwich, Barnstable Co., Mass.; Silas S. Snider, Chicago; Frederick F. Tisdall, Toronto.

Emeritus: R. S. Friedley, Akron; Elmer G. Horton, Columbus; James H. McKee, Philadelphia.

Respectfully submitted,

CLIFFORD G. GRULEE, *Secretary*

The Treasurer's Report was presented as follows:

STATEMENT OF RECEIPTS AND DISBURSEMENTS
JULY 1, 1948 TO JUNE 30, 1949

Balance in checking a/c—July 1, 1948		$ 18,974.49
Balance in savings a/c—State Bank & Trust Company		15,708.99
Balance in savings a/c—First National Bank & Trust Co.		9,176.50
		43,859.98
Receipts		
Dues	$66,273.14	
Exhibits—Milwaukee, Wis., June 1948	100.00	
Seattle, Wash., Sept. 1948	1,887.50	
Atlantic City, N.J., Nov. 1948	12,720.00	
Atlanta, Ga., April 1949	5,225.00	
Areal Meeting—Milwaukee—Registration	1,018.75	
Seattle—Registration	735.00	

Seattle—Cash taken in		1,400.00
Atlanta—Registration		5,336.00
Annual Meeting—Atlantic City—Seminars		6,825.00
Registration		14,419.53
Round tables		3,948.00
San Francisco, Calif.—Seminars		3,250.00
First Pan-American Congress—Sept. 1947 Expense. Check cancelled and restored to account in 1949		150.00
Initiation Fees		8,350.00
Interest Earned		848.32
International Congress Assessment		80.00
Committee—Improvement of Child Health		71,775.00
Pamphlets—Child Health Record	$ 434.94	
Immunization Procedures	251.69	
Newborn Manual	1,480.09	2,166.72
PEDIATRICS		23,795.00
PEDIATRICS—Special Account		6,038.74
Interest Earned on Special Account—1st Nat'l.		91.99
		236,433.69
		$280,293.67

Disbursements

Annual Meeting—Dallas, Dec. 1947	$	175.50
Atlantic City, Nov. 1948		24,804.95
San Francisco, Calif., Nov. 1949		569.88
Areal Meeting—Buffalo, N.Y., April 1948		236.40
Milwaukee, June 1948		2,672.52
Seattle, Sept. 1948		3,911.57
Atlantic, April 1949		7,368.95
Bank Charge & Exchange		73.36
Certificate Expense		168.18
Executive Board		10,194.57
Meetings—General		12.25
Miscellaneous		583.01
Office Supplies and Equipment		893.34
2nd Pan-American Congress		300.00
PEDIATRICS		24,305.00
PEDIATRICS—Special Account		2,159.80
Postage		904.14
Rent		2,737.62
Salaries—Secretary	$18,000.00	
Ass't Secretary	5,000.00	
Office	10,635.84	33,635.84
Stationery and Printing		3,263.29
Telephone and Telegraph		661.53
Travel Secretary		1,631.34
Treasurer's Bond		322.50
Expense—Districts	349.82	
State	141.72	
Committees	64,404.16	64,895.70
Pamphlets—Child Health Records	496.84	

Immunization Procedures	17.98		
Newborn Manual	1,234.09	1,748.91	
Refund to Mead Johnson & Co. for unused portion of sum allotted for Post War Courses		4,345.40	192,575.55
Balance—June 30, 1949			$ 87,718.12
Balance in checking a/c—June 30, 1949			54,197.32
Balance in savings a/c—State Bank & Trust Co.			24,252.31
Balance in savings a/c—First National Bank & Trust Co.			9,268.49
			$ 87,718.12

(The fiscal year report has been substituted for the 11 month report which was accepted by the Executive Board.)

Many phases of the Treasurer's Report were discussed. The Treasurer reported that the Academy was nearly up to the $70,000 mark which was set the year before as a necessary reserve fund.

It was moved, seconded and carried that the Reports of the Secretary and Treasurer be accepted.

It was moved, seconded and carried that the Report of the Budget Committee be accepted. The Budget Committee submitted without recommendation the budget as proposed for the Committee on Improvement of Child Health.

The following recommendations made by the Budget Committee were accepted:

1. The Budget Committee recommends that the Executive Board empower the Secretary to lease suitable space for a period of three years at an estimated cost of $375.00 per month and that the Secretary be empowered to make such improvements as may be necessary.

2. The Budget Committee recommends that the Treasurer be empowered to transfer such profits as have accrued from the Seattle, Wash., Atlantic City, N.J., and Atlanta, Ga., meetings, and in addition such savings as have been made over and above the budget for the year 1948-1949, in accordance with the action of the Executive Board meeting in Milwaukee, Wis., June 26-27, 1948.

3. The Budget Committee recommends that the Secretary be authorized to have a Certified Public Accountant audit the accounts of the American Academy of Pediatrics as of June 30, 1949.

The budget of PEDIATRICS was thoroughly discussed and it was moved, seconded and carried that it be accepted.

The following District Reports were presented and accepted:

District I: In Connecticut our report is in the printer's hands and as of four days ago was completely printed, with the exception of the appendix; the report should be in the mail within the next week. The State Medical Society, at the meeting of the House of Delegates in the spring, authorized the establishment of a Committee for the study and implementation of the results found in the State by the Study.

Respectfully submitted,

OLIVER L. STRINGFIELD, *Chairman*

District II: During the past year, activities of the District have been mainly concerned with the Survey itself. The complete record of the data collected in this state has now been published and widely distributed. It contains in a readable style all of the facts that were gathered during the Survey, which was conducted not only by the questionnaire method, but also by the sample method. That data have originally been divided into two parts: those activities which are carried out in the metropolitan district of New York City and those activities which are carried on in the upper part of the state. Many recommendations were made which will be implemented as time goes on.

As a result of this Survey the six counties, including and surrounding Buffalo, have had a minute survey showing the type of work that is going on in that part of the state as compared to other parts of the state and elaborated in much more detail than the state report. A similar survey is being made for Rochester and the 11 counties that surround it. The survey in Buffalo will be published this fall, that in Rochester probably a few months later.

During the year we held within our district the banquet celebrating the completion of the

national Survey. It was held at the Hotel Roosevelt and, while details of this meeting are given elsewhere, it might be said that it was not only a success in itself, but it was a tremendous success in that it called the attention of the nation to the work that the Academy had been doing.

In order to carry out the recommendations that have been made by the Executive Board that the membership be better acquainted with its deliberations, meetings will be held in October with that purpose in mind. The upstate group will meet during the month in Rochester and those things which have been discussed by the Executive Board, and will be discussed by them in the annual meeting in San Francisco, will be laid before the group by the District Chairman. A similar meeting is being planned for New York City. It is hoped in this way that the membership can be acquainted not only with what has been done but what is being planned by the Executive Board so that their opinions may have influence on its deliberations.

Respectfully submitted,

PAUL W. BEAVEN, *Chairman*

District III: There are two main projects in the three states of District III: one, the completion of the state reports and, two, the organization of the decentralization program.

So far as state reports are concerned, Dr. Lathrop informs me that the New Jersey report is in the hands of the printer and will soon be distributed to every member of the New Jersey State Medical Society.

The organization of the New Jersey State Academy group has been started and the nominating committee has proposed Dr. Frederic W. Lathrop for Chairman; Dr. William F. Matthews as Vice or Alternate State Chairman; and Dr. Walter L. Mitchell, Jr., as Secretary and Treasurer, all for three years.

The Delaware State Report is still in the hands of the author.

The Pennsylvania Report is almost completed and should reach the printer this summer. Dr. William W. Briant, Jr., has been elected Western State Chairman for a three year term.

The decentralization program is about to hatch. Briefly, it is planned to do three things: (1) to rotate pediatric residents from teaching hospitals on short terms in good hospitals not yet recognized for residency training; (2) to exchange residents from recognized training hospitals with the teaching hospitals; (3) to set up a pool of third year residents who may be used in hospitals not ready for recognition as training centers.

In addition to this there will be a program of conferences and supervision of the resident in the peripheral hospitals.

Several hospitals have expressed interest in this program. We intend District III to be a pioneer in combining the resources of several medical schools for a widespread program of medical training.

Respectfully submitted,

PHILIP S. BARBA, *Chairman*

District IV: No Report.

District V: Dr. Wishropp did not send a written report, so I will sum up from two letters here.

Dr. Carlo, State Chairman of Indiana, writes that they had their preliminary meeting in May and will have a meeting in October for the final organization of the Indiana Chapter.

Dr. Kramer, State Chairman of Ohio, in a letter states that the Ohio pediatricians met at the time of the Ohio State Medical meeting and appointed a committee at that time to look into the question of organizing a chapter in Ohio. That committee met and it advised the formation of a chapter, and drew up a tentative constitution, which also is to be acted upon at the next meeting of the Ohio State Medical Association, which will be held next spring.

The idea of the Ohio Chapter will be to have an all-day and evening meeting, the morning session being that of the Pediatric Section of the Ohio State Medical Association, the afternoon devoted to a clinical meeting, and the evening to the business side of the chapter.

Since the Ohio State Medical Association meets in the three largest cities in Ohio, rotating, Cleveland, Columbus and Cincinnati, it is hoped that the pediatric departments in the schools in those cities will put on a clinical program.

There is a question here on whether the American Academy of Pediatrics has instructions for

the local representatives of the State White House Conference groups that are going to be organized. Ohio has its committee organized for the 1950 White House Conference. There were some 120 invited to that first meeting. Out of that they have appointed an executive committee of 18, which will formulate the program. Two of those 18 are Academy members. One is Dr. Kramer, the Ohio State Chairman, and the other is Dr. Shafer, who is Chairman of the School Health Committee.

Another thing that the state group accomplished is closer cooperation with the P.T.A. in working out a better method of the preschool examinations. As they are held generally now in Ohio, they are done at the round-ups, which is unsatisfactory. So the State Chairman of the Committee on Cooperation with the P.T.A., Dr. Charles L. Shafer of Mansfield, is organizing a program in his county, working with the P.T.A., of having children go to the private physician's office for the examination, and, where the children come from indigent families, to arrange for that at the Child Health Conference or clinic where they will be available.

A suggestion comes from another of the Ohio members, the question of whether the Academy committee working with the P.T.A. ought to try to streamline the P.T.A. forms. As they are now, they are not felt to be satisfactory.

In regard to the Child Health Survey report, we are having two reports, both of which ought to be in the mail in September or October. The three installments of the detailed report have appeared in the *Ohio State Medical Journal*. The conclusions and recommendations we hope to print sometime later, and they will be put together as one report and sent out to each doctor in Ohio.

Then there is a popular report, which is going to be a good one, which will be sent to every physician and dentist in the state. It is a pictorial report, and is extremely well done. That, too, will be ready for distribution in September or October.

The State Committee on Fetus and the Newborn, headed by Dr. Victor Greenebaum, has worked closely with the State Department of Health, and has been instrumental in adding several items to the code for the regulation of maternity departments; and, second, there was a suggestion by Dr. Kramer to reduce the initiation fee for full time members.

Respectfully submitted,

BENJAMIN HOYER, *Alternate Chairman*

District VI: Reports have been received from four states concerning Academy activities.

Dr. Zimmerman, South Dakota, has had numerous requests for the State Child Health Survey report, which is now complete. The State Medical Society Executive Secretary has been approached concerning the possibility of placing a pediatrician on the State Licensing Board. No definite reply has been given.

Dr. McEnery, Illinois, reports that the State Child Health Survey report will soon be available. At the present time it is awaiting the approval of the *State Medical Journal*. Dr. Poncher's recent illness has delayed earlier publication of the report. The Academy manual on hospital nurseries has been fairly well distributed throughout the state, and pediatricians of the state are requested to encourage the use of this manual in all hospital nurseries with which they have a contact.

A State Academy Advisory Committee, consisting of Drs. J. F. Carey, G. Clike, W. L. Crawford, G. Drennan and J. Hess has been appointed. The chief duty of this Committee will be to implement the findings of the Child Health Survey.

An effort is being made to place a pediatrician on the State Licensing Board.

Dr. Peterman, Wisconsin, reports that effort is being made to initiate the recommendations of the Academy Newborn Nursery Manual in hospitals throughout the state.

The Academy members on the committee of the Governor's Health Conference held in May and Academy members cooperating with the Milwaukee County Medical Society initiated a special program for May Day, Child Health Day and National Baby Week. Dr. Charles Hendee Smith gave several lectures to a combined meeting of pediatricians, obstetricians and supervisors of newborn nurseries as part of this program.

The state group has also been active in organizing a program for the care of the cerebral palsied child. As part of this program Dr. George G. Deaver conducted a series of lectures and clinics in this field over a period of two days, to which all interested persons were invited. A later meeting is to be arranged for October, at which it is planned to have Dr. Winthrop Phelps conduct a similar

series. This meeting is to be held in conjunction with the regular meeting of the Wisconsin Medical Society.

Dr. Nutting, Minnesota, has initiated a move to effect closer organization of the Academy members in the state. To accomplish this purpose a special meeting will be held in July or August.

The State Child Health Survey report is now well under way after some delay, and publication is expected soon.

The Minnesota State Medical Association has been requested to place a pediatrician on the State Licensing Board.

Respectfully submitted,

GEORGE F. MUNNS, *Chairman*

District VII: Since the last report, there has been quite a bit of progress made in the formation of the chapters of the various states. Elections were made before the last meeting, in Alabama, Tennessee, Louisiana and Texas. Missouri has formed its chapter and has a state chairman.

Some of the fellows are discussing more close cooperation between the state pediatric societies and the state medical associations. One has suggested that we ask the President of the state pediatric society to work more closely with the Academy in carrying out the suggestions and the findings of our Study.

There is a great deal of overlapping in all of our activities; more coordination of effort in our state pediatric society, as well as our state medical associations, to carry out the findings would be a great help.

We are having refresher courses in practically every one of the states. There has been quite a bit done for the physical examination for the preschool child, so that they have the entire summer to clear up any of the defects that are found. We are having some interesting work done by a Committee on Children and Youth in the various states, and we have done quite a bit on the planning of the White House Conference in 1950.

In Texas we have just recently opened three premature nurseries, which will act as centers for the teaching care of the premature infant. We feel that we have been making definite strides forward.

Respectfully submitted,

THOMAS J. MCELHENNEY, *Chairman*

District VIII: A considerable number of new members have been added during the year in District VIII. There is a good deal of member interest in the Academy affairs. Formal organization of the membership at the state level is progressing and already each state has elected a chairman. Many new state chairmen are noted in this list and we expect a good deal from each of them.

A number of state reports have been or are now about to be published. California members are currently concerned with preparations for November meetings in San Francisco.

Respectfully submitted,

CRAWFORD BOST, *Chairman*

District IX: All the states in this district have been active in making preparations for the Second Pan-American Pediatrics Congress which will be held in Mexico City next November.

The General Assembly of District IX will be held at the same time as this Congress, because this is the only occasion for all the Latin American group to meet, if you consider that some states are so far away as Chile or Argentina and the traveling expenses are very high.

District IX has presented to the Executive Board a motion to modify the election system of District IX, proposing a particular regulation more adaptable to the special organization of the Latin countries.

The membership of District IX want to express their particular interest in the job accomplished by Dr. Grulee as the principal base of the actual development of the Academy; therefore, we believe that any project of reorganization must maintain the position of the Executive Secretary by Dr. Grulee, and, if Dr. Grulee wishes to retire at any time, that he should be appointed Honorary Life Secretary with the right to receive a life pension.

Another special recommendation to the Committee on Reorganization is presented in a separate statement.

Respectfully submitted,

FELIX HURTADO, *Chairman*

A letter to Dr. Sisson was read as follows:

"I have the pleasure of advising you, in the capacity of President of the American Academy of Pediatrics, of the decision of a committee of the American Public Health Association, under the chairmanship of Dr. George Baird, who awarded the American Academy of Pediatrics a Lasker citation, in recognition of the public health significance of its nationwide Study on Child Health Service in Pediatric Education. This award will be presented at the time of the 77th Annual Meeting of the American Public Health Association to be held in New York City on the evening of Tuesday, Oct. 25, and the place is the Manhattan Opera House."

Dr. Henry F. Helmholz suggested the appointment of two members from the American Academy of Pediatrics as representatives on the American Committee for the Sixth International Congress. Dr. Sisson appointed Dr. Oliver L. Stringfield and Dr. Rustin McIntosh.

The Secretary read a letter from Dr. McLester as follows:

"A Committee has been organized for the purpose of placing the name of William Crawford Gorgas in nomination for the New York University Hall of Fame for Great Americans. The names of only two members of the medical profession have been placed in this Hall of Fame.

"The Medical Association of Alabama, in its meeting in April, 1947, passed a resolution authorizing the officers to nominate Dr. Gorgas at the proper time, and a similar resolution was passed on the 12th of June, 1947, by the American Medical Association. A number of other associations and societies have also passed such resolutions.

"We are advised by Dr. James Rollin Angell, Director of the Hall of Fame, that nominations will be received at any time, but preferably after April 1, 1949, and thereafter at any time during the ensuing year. I hope you will consider this movement in behalf of the Academy of Pediatrics, and you will concur in our efforts. If you can do this, we shall appreciate your so advising the elector or electors from your state, Illinois, or any other with whom you may wish to communicate. Please send a copy also, advising content of your resolution to Dr. O. C. Carmichael, chairman of the Committee, at the address indicated on the letterhead. Also please advise Dr. T. W. Martin of Birmingham, Ala., Vice-Chairman of the Committee, as we are endeavoring to keep a full record of these proceedings, in both Dr. Carmichael's and Dr. Martin's office.

"You may wish to review the service of Dr. Gorgas. Therefore, you will find enclosed a copy of the address by Dr. Martin before the Alabama New Common Society in 1947.

"Trusting that you will take part in the effort, I am—"

It was moved, seconded, and carried that the Academy endorse the effort to have the name of Dr. William Crawford Gorgas inscribed in the Hall of Fame.

The Secretary read the following letter from Dr. A. C. Ivy, from the National Society for Medical Research:

"Your organization is one of the few scientific groups in the United States that is not at present officially associated with the National Society for Medical Research.

"In its cooperation to build public understanding of medical research, the NSMR was organized under the sponsorship of the Association of American Medical Colleges in 1946. It is essentially a federation of over 200 organizations. Its current program is outlined in the enclosed annual report. Participating national associations also are listed.

"We would like to extend an invitation to your organization to become a member organization of the NSMR. There are no dues. However, the Society's program is supported by contributions from its member groups, ranging from $25 to $1000 and by contributions from commercial concerns.

"Whether or not your organization can contribute to the financial support of the Society's program, we would like to have your active cooperation as a member society.

(signed) A. J. Carlson
A. C. Ivy."

It was moved, seconded, and carried that the Academy join this group but that at the present the Academy is not in a position to contribute to the funds of the organization.

The question arose of the printing of a list of exhibitors and contributors to the advertising in PEDIATRICS to be compiled and sent to the members of the Academy. It was decided to do this at the first of the year. The Secretary was instructed to have this list put on a card and sent out with the Fellowship Lists.

The Secretary announced that the Annual Meeting had been planned for next year at the Palmer House in Chicago and the Areal Meeting next spring, 1950, at Philadelphia. Several meeting places were discussed and the matter of where areal meetings and annual meetings should be held was left at present in the hands of the Secretary. It was decided that for the next year or two we would have one areal meeting and the annual meeting.

The question of whether in the future all meetings should be held in Chicago as requested by several of the members was discussed, but for the present no decision was arrived at.

The evening session convened at 8 p.m., President Sisson presiding. The following committee reports were presented and accepted:

COMMITTEE ON COOPERATION WITH THE AMERICAN LEGION

At the Atlantic City meeting of the Academy, the Executive Board authorized a new line of action with regard to liaison with the American Legion. The new departure was to consist of direct efforts to stimulate the Legion to undertake projects and make efforts aimed at correcting deficiencies in child health services and pediatric education, such as have been revealed by the recent survey. The central purpose was to bring the potentially powerful forces of the Legion into the effort to correct the deficiencies. The previous policy had been a purely advisory one.

In line with this new policy, the Chairman of the Committee on Cooperation with the American Legion was appointed by the Legion as an advisory member of its National Child Welfare Committee, and attended the recent meeting of this group in Indianapolis, April 21-23. Advisory membership on the Commission permits the Academy to have a representative in the group which sets the national child welfare policy for the Legion. It is of value from the standpoint of learning what is being planned and in furnishing the opportunity to put forward ideas for new plans. It permits the Academy to have representation at the top level of Legion child welfare activity.

In view of the above facts, I made certain recommendations to the Committee at the recent meeting in Indianapolis. Copies of the remarks made have been sent to Dr. Sisson, Dr. Grulee and Dr. Hubbard.

The Committee's attention was called to the Study of Child Health Services and Pediatric Education. Emphasis was given to the recommendation of the Committee for the Improvement of Child Health that one of the first necessities is to improve pediatric educational facilities, especially for general practitioners in rural and isolated areas. It was urged that a sum of $10,000 be allocated to sponsor demonstration postgraduate pediatric programs in one state in the southeastern area and one in the southwestern area—the regions shown by the survey to be most deficient in child health facilities. Under the plan, $5000 would be made available in one state in the southeastern area and $5000 to a state in the southwestern area. Each state would have to match the funds, so that a total of $10,000 would be available in each state selected. The programs would be planned by the state pediatric societies. The Academy would participate in looking over plans from various states and helping decide, along with representatives from the Legion, which states seemed to have the best plans and needed the programs the most.

At the same time, it was recommended that the sum of $6000 be set aside for pediatric residency scholarships, the sum of $1000 a year for two years being granted to three promising young physicians who needed financial help in securing their pediatric training. The Academy would select the candidates. Emphasis might well be given to awarding the scholarships to promising young men who agreed to practice in smaller communities, or more isolated areas. Arrangements might be made to the effect that the recipient did not have to repay the money if he continued for a certain time to practice in a smaller community, but he would be required to repay the grant if he changed his mind while in training and failed to carry out his part of the bargain.

A third recommendation was to the effect that a member of the Academy in each state be included on the state's American Legion Coordinated Child Welfare Committee, which is the planning body at the state level for child welfare activities in the state.

The National Child Welfare Committee discussed these three recommendations. Money is not now available from the National Child Welfare Division's regular budget, and will have to be sought from other Legion sources—probably the Auxiliary.

The attached resolution (No. 57, Advancement of Education and Training in Pediatrics) was secured, and may be useful in at least setting the policy of endorsing such plans. This might prove useful if other groups of the Legion, such as the Auxiliary, decide to make the funds available, as I believe they will. The incoming President of the Auxiliary, whose term begins this summer, is Mrs. Norman Scheehe, of Rockford, Ill., and she is extremely interested in these plans for pediatric education.

The second attached resolution (No. 58, Cooperation of Departments [States] with American Academy of Pediatrics) will probably serve a useful purpose in urging closer state liaison.

Earlier this month, in Atlanta City, Dr. Sisson, Dr. Hubbard and I met together and discussed all of these matters. Dr. Hubbard and I have been in close contact since then. It is planned for Dr. Hubbard to be present also at the next meeting of the Committee in Philadelphia in August, so that he can personally take part in the meeting with the Committee. Incidentally, an item on the agenda is a detailed analysis of the chief findings of the Study of Child Health Services and Pediatric Education. It will be very helpful to have Dr. Hubbard at the meeting.

In summary, advisory representation on the National Child Welfare Committee has been achieved, members of the Committee have been indoctrinated to some extent with the deficiencies in child health services and pediatric education, thoughts have been channeled toward a definite sum of money for a definite purpose, the incoming President of the Auxiliary is eager to obtain the money from her group, Dr. Hubbard has been brought into the picture so that the whole matter may be tied closely to the Committee for the Improvement of Child Health, and there is promise of better liaison at the state level. The next step is to concentrate on obtaining the money for two demonstration projects in postgraduate pediatric education and for three pediatric residency scholarships, preferably for men who will agree to practice in smaller communities.

EXECUTIVE COMMITTEE, NATIONAL CHILD WELFARE DIVISION, THE AMERICAN LEGION

In Meeting, National Headquarters
Indianapolis, Ind.
April 21-23, 1949

No. 58. Cooperation of Departments with American Academy of Pediatrics. (Presented from floor by National Vice Chairman Dr. A. H. Wittman.)

"WHEREAS, The Child Welfare Commission and Division have been authorized for a number of years to maintain cooperative relations with the American Academy of Pediatrics, and

"WHEREAS, The American Academy of Pediatrics has established a nationwide system of Liaison Representatives with the American Legion, and

"WHEREAS, The American Academy of Pediatrics has recently completed a nationwide Study of Child Health Services and the information secured through this study is of great value in the determination of future activites in the field of child health, now, therefore, be it

"*Resolved,* That all Department Coordinated Child Welfare Committees of the American Legion be urged to contact the American Academy of Pediatrics Liaison Representative with the American Legion in each Department and to invite such representatives to attend meetings of the Department Coordinated Committees and to participate in the development of needed programs for the improvement of child health.

"Approved:

(Signed) David V. Addy
National Child Welfare Chairman
The American Legion."

EXECUTIVE COMMITTEE, NATIONAL CHILD WELFARE DIVISION,
THE AMERICAN LEGION

In Meeting, National Headquarters
Indianapolis, Ind.
April 21-23, 1949

No. 57. Advancement of Education and Training in Pediatrics. (Presented from the floor by member Charles M. Mitchell.)

"*Resolved,* That the Commission go on record as endorsing in principle the furtherance of postgraduate education of physicians in diseases of children in the areas where such training is most needed and further endorses the principle of securing scholarships for training of young physicians in the field of pediatrics.

"Approved
(Signed) David V. Addy
National Child Welfare Chairman
The American Legion."

Respectfully submitted,

JAMES G. HUGHES, *Chairman*

COMMITTEE ON SCHOOL HEALTH

In accordance with our telephone conversation May 2, I traveled to Atlantic City on May 4 to attend a conference on the desirability of an authoritative statement on the implementation and limitations of school health services provided in S 1411. This Bill which provides assistance to states in the improvement of health services in schools was passed unanimously in the Senate April 29 and presumably will be passed in the House.

Present at the Conference, held at 8 p.m., May 5, in the Marlborough-Blenheim were the following individuals:

Warren R. Sisson	Allen M. Butler
Grover F. Powers	Ralph V. Platou
Albert D. Kaiser	Roger L. J. Kennedy
James L. Wilson	John P. Hubbard
Harry H. Gordon	Myron E. Wegman
Paul A. Harper	Leona M. Baumgartner
Miner C. Hill	Thomas E. Shaffer

The meeting was an informal conference to discuss the basic requirements in school health services and to talk over plans for arriving at a statement which would guide state health and educational agencies in drawing up a state plan.

Drs. Harper and Baumgartner are members of the American Public Health Association Committee on Child Health and represented that organization informally. Drs. Sisson, Kaiser and Shaffer assumed responsibility for representing the Academy (Dr. Kaiser and I are on the Committee on School Health); Drs. Wilson, Powers, Kennedy and Hubbard had been invited as members of the ICH Committee. The others came as Academy members without official interest in the problem.

After much discussion about the extent of corrective services which could be provided with $35,000,000 and the most basically important services which should be incorporated, it was agreed that a joint statement by the Academy and the A.P.H.A. would be desirable. Dr. Harper and I were designated to draw up such a statement. Dr. George M. Wheatley was later named as an additional consultant on this assignment. At present Dr. Harper and I are working on a draft and I hope we can have it finished before the Executive Board meeting in June. I do not think it will be ready to submit to you by May 28, yet it will come as a report from our Committee on School Health. I shall plan to send it in as quickly as possible for consideration.

Respectfully submitted,

THOMAS E. SHAFFER, *Chairman*

This was accepted as a preliminary report.

COMMITTEE ON FETUS AND NEWBORN

There has been some activity by State Sub-Committees on Fetus and Newborn, but not as much as we would like. We will try to stimuate more activity this summer.

The distribution of the Academy's manual on "Standards and Recommendations for the Hospital Care of Newborn Infants" has been as follows:

1000 copies donated by Borden—Distributed 900

5145 copies First Printing of A.A.P.

Distributed to Members	2460	(free)
Sold to Members	215	
Sold to Nonmembers	2696	
(250 of which will go out from second printing)		
5000 copies Second Printing of A.A.P.		
(Not as yet received from printers) Distributed Free	0000	
Sold (Nonmembers)	250	
As of June 1, 1949, we have		
Copies on hand	58	
Cash received from sale of Manuals	$1427.09	
Cost of printing and distributing Manuals	$1215.56	

Respectfully submitted,

STEWART H. CLIFFORD, *Chairman*

COMMITTEE ON HOSPITALS AND DISPENSARIES

For the November meeting it is planned to have a report which will encompass the following: 1. A critique of the Chapter IV (Hospitals) of Child Health Services and Pediatric Education. 2. An analysis of the various government bulletins on construction of pediatric units in general hospitals. 3. Possibly some comments on recommendations concerning problems of nursing in pediatric hospitals if this falls within the province of the committee.

Respectfully submitted,

AIMS C. MCGUINNESS, *Chairman*

COMMITTEE ON IMMUNIZATION AND THERAPEUTIC PROCEDURES FOR ACUTE INFECTIOUS DISEASES

For several months past, I have been working on a revision of the "Red Book" and have almost completed my first draft.

Undoubtedly, replies from all members of our committee will not be in my hands by June 24, when the Executive Board holds its next meeting in the Palmer House, Chicago; consequently it does not seem likely that my final report will be ready by that date.

Respectfully submitted,

ARCHIBALD L. HOYNE, *Chairman*

COMMITTEE ON MEDICAL EDUCATION

The activities of the Committee on Medical Education during the first half of the year 1949 have been confined to the attendance of Dr. Lawson, representing the Committee, at a meeting of the National League of Nursing Education.

At the above meeting Dr. Lawson presented a paper on "The Education of Nurses in the Problems of the Newly-born Infant," which will probably be published in the *American Journal of Nursing*. A copy of Dr. Lawson's detailed report on the above meeting is attached.

Respectfully submitted,

JOHN MCK. MITCHELL, *Chairman*

Report of Dr. Lawson, representing Committee on Medical Education at the meeting of the National League of Nursing Education:

As an outgrowth of some correspondence with Adelaide A. Mayo, Executive Secretary of the National League of Nursing Education, Dr. J. McK. Mitchell asked me to serve as the representative of the Academy of Pediatrics Committee on Medical Education to the pediatric subcommittee of the Curriculum Committee of the National League of Nursing Education. The National League of Nursing Education, through its Curriculum Committee, is at present beginning to make an over-all review of its "Curriculum Guide" which is used in most nursing schools of this country.

As a preliminary to the review of the pediatric nursing curriculum, a joint meeting was called with the subcommittee on obstetric nursing to discuss the field of "the beginning of the new family through one month of age of the newborn, including prematurity and allied clinical conditions of the newborn." The Chairman of the pediatric subcommittee, Miss Isabelle M. Jordan, wrote to ask if I would give an hour discussing to the combined committee on the relation of pediatric medical education to pediatric nursing education and specifically requested discussion of "growth and development and mother-child relationships . . . prematurity . . . anomalies . . . anemias . . . infections."

This was a three day meeting composed of these two subcommittees and attended by various instructors and administrators of children's hospitals and maternity instructors and a couple of pediatric nursing consultants from state health departments. Miss Jordan, the chairman, is a member of the Children's Bureau staff. Dr. John Parks, Professor of Obstetrics of George Washington University, spoke on obstetric problems. Also present were Dr. Katherine Bain and Dr. Henry Work of the Children's Bureau. Since the second two days were devoted to small group meetings of the nursing committees, it was not felt necessary for me to be present beyond the first day.

Under the general directive of Miss Jordan's request, I gave essentially the material in the enclosed paper and discussed in an informal way problems that were raised by it. In general, my main thesis was that nursing schools should not try to get too much detailed knowledge of disease processes into the students, as much as a general knowledge of children, and an appreciation of their behavior in health as well as illness. I felt that detailed knowledge of disease could wait on experience and postgraduate study.

I am still somewhat confused as to what was actually accomplished at this meeting. There is apparently a fair amount of conflict among the various branches of nursing as to "what belongs to whom" so that my own education into the problems of nursing education is just beginning! There was a tendency on the part of some of the nurses (obstetric, I think) to make an issue of minor points and to imply that the nursing problems would not be so bad if the doctors would not keep adding new duties to their load (the giving of penicillin shots, for example). There seemed to be some fear that the doctors were trying to tell them how to run their own programs. However, I believe we were able to show even these skeptics that our interest is a mutual one in improving the nurses' education, and that we were only trying to help them see where our problems were mutual. It will take time and further contact with this group to tell how valuable will be our cooperation.

In closing, I would appreciate the expressions of the other members of the Committee on Medical Education and other interested members of the Academy on this problem. Nursing education is important to the pediatric group, but is a field in which most of us have little concrete experience.

Respectfully submitted,

ROBERT B. LAWSON

SECTION ON MENTAL GROWTH AND DEVELOPMENT

The officers of the Section on Mental Growth and Development of the Academy, through correspondence with each other, have been considering candidates for membership in the Section and have been formulating plans for future endeavors in Academy affairs. The policies suggested have not been clarified sufficiently to be presented in the form of recommendations to the Executive Board. The officers of the Section hope that progress will continue so that at the November meeting a more detailed report may be presented.

Respectfully submitted,

MILTON J. E. SENN, *Chairman*

COMMITTEE ON PAN-AMERICAN SCHOLARSHIPS

No report was given, but a letter from Dr. Helmholz was read, stating that he was making efforts to revive these scholarships.

PROGRAM COMMITTEE

The report of this Committee was delivered by Dr. Martmer and among other things brought out the fact that the members had been asked to give papers at the meeting and the response had been gratifying.

COMMITTEE ON GEOGRAPHICAL DISTRIBUTION OF PEDIATRICIANS

The Committee continues to prepare geographic surveys for the men who are searching for location for their pediatric practice. Requests for such surveys are coming in from various parts of the U.S.A.

The information on any particular location ought to be as complete as it is possible to collect. Information on the total population and child population as well as on the social, religious and economic characteristics of the locality in question is desirable. Such information is available in part from the statistical records of the U.S. Board of Census, but it is not up to date except for some sample metropolitan areas that were surveyed in 1947 for population characteristics and published in 1947.

In the further development of this study, we are hoping to add this kind of information to these surveys.

Respectfully submitted,

OTTO L. GOEHLE, *Chairman*

COMMITTEE ON CARE OF EUROPEAN CHILDREN

The activities of the Committee are confined to the medical supervision of groups of children arriving in this country in cooperation with the United States Committee for the Care of European Children.

Increasing numbers have come recently under provisions of the Displaced Persons Act. Your committee has assumed the entire responsibility for every phase of medical care and emergency that arises in connection with these children while they are housed in the Reception Centers in New York City and before they are transferred to agencies throughout the United States.

Medical care includes physical examination, Schick, tuberculin, Wassermann tests and chest roentgenogram. A second reception center was opened following an epidemic of mumps in the first center.

A variety of problems present themselves constantly and experts in various fields have been consulted. These physicians, both members and nonmembers of the Academy, have given of their services freely and willingly.

Since January 1949, 166 boys and girls have come to the United States from the United States, British and French zones of Germany and Austria.

Their countries of origin are as follows:

Austria	3
Estonia	3
Germany	11
Latvia	102
Lithuania	11
Poland (Ukraine)	7
Roumania	1
Russia (Ukraine)	3

Yugoslavia	24
Unknown	1

Additional groups of children are still being examined.

Respectfully submitted,

CARL H. SMITH, *Chairman*

COMMITTEE TO COOPERATE WITH THE UNITED STATES FOOD AND DRUG ADMINISTRATION

The Committee to Cooperate with the United States Food and Drug Administration held a meeting in Atlantic City in November 1948, subsequent to the meeting of the Academy so that no report could be obtained.

At this meeting a number of problems relative to misuse of medications and drugs were presented by Dr. Kerlan. None of them were of the order for which direct action could be taken by other than educational means. It was the sense of the group that one or more articles dealing with this problem might well appear in one of the medical journals. On the basis of this decision, Dr. J. Judd Shields of Philadelphia has been requested to prepare such a paper. He is now in the process of doing this.

The committee recently appointed by Dr. Sisson has not met. To date, there have been two communications from Dr. Kerlan which have been answered.

Respectfully submitted,

WALDO E. NELSON, *Chairman*

LIAISON COMMITTEE TO MEET WITH THE AMERICAN MEDICAL ASSOCIATION

Subsequent to the Atlanta meeting of the Executive Board this committee was appointed to meet with a similar committee from the American Medical Association. The AMA Committee consists of Drs. Walter B. Martin, Norfolk, Va., and Joseph S. Wall and Margaret Mary Nicholson of Washington, D.C.

On May 25th we received through Dr. Sisson a letter from Dr. Clarence H. Webb, of Louisiana, in which he reported that the Louisiana State Medical Society had withheld action on recommendations resulting from the State Child Health Study until after the June meeting of the AMA. This attitude, he felt, resulted from the reports of Louisiana delegates of the November meeting of the AMA that there was criticism of the Academy of Pediatrics not only because of the recommendation for Federal support of Pediatric education but also of the whole Child Health Study. He felt that action should be taken to clear up this misunderstanding.

Copies of this letter were sent to each member of our committee and to each of the AMA committee. There was a covering letter describing the meeting with the Board of Trustees in February and the setting up of the two committees. Responses were immediate and it was arranged to have a joint meeting of the two committees at the AMA convention. Dr. Martin promised his support.

The first meeting, 6-9-49, was attended by Drs. Martin; Nicholson; Crawford and Stringfield (the latter, a member of the overlapping Public Relations Committee, substituting for Dr. Barba.). At this meeting the following resolution was formulated:

* "WHEREAS, The American Academy of Pediatrics has a particular interest in Child Health; and

"WHEREAS, It is recognized that certain deficiencies exist in this field; and

"WHEREAS, It is desirable that definite programs be set up on the State and local level to correct these deficiencies where they exist; and

"Whereas, the American Academy of Pediatrics has gone on record as opposed to Senate Bill 5 or any similar bills proposing to estabish a system of socialized medicine; therefore be it

"*Resolved*, That the American Medical Association favor the development of sound child health programs on the state and local level by pediatric groups working in cooperation with the several

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* Material between asterisks, from the report of the Liaison Committee, has been submitted to the members of the Academy through the State Chairmen.

state medical associations and the local component county societies and in conformance with the Principles of Medical Ethics and Practice as laid down by the American Medical Association."*

This resolution was presented by Dr. William Weston, Delegate from the Section on Pediatrics, and was passed by the Reference Committee and subsequently by the House of Delegates. Dr. Crawford announced this action of the House of Delegates to the Section on Pediatrics.

Other topics were discussed at a subsequent meeting of the two committees, attended by Drs. Martin, Nicholson, William Weston, Jr., and Barba.

The action of the House of Delegates in flatly rejecting the School Health Bill was discussed. It should be pointed out that the Board of Trustees felt this action of the House to be unwise in that there were certain good features in the Bill, and the objection of the AMA has already been stated by Dr. Miller of the Board of Trustees, in Congressional hearings on a similar Bill the preceding year. These objections, in general, were in accord with objections raised by representatives of the American Academy of Pediatrics. The action of the House was modified to the extent that the Board of Trustees was permitted to point out the true position of the AMA in this matter.

The subject of separate examinations in pediatrics by the various State Boards was discussed. It was pointed out that such procedures were matters of state government. The most we could do was to ask the House of Delegates to pass a resolution encouraging the state societies to work on the problem.

At a subsequent meeting of the Pediatric Section it was moved, seconded and passed that the Delegate of the Section be instructed to introduce the following resolution at the next (December) meeting of the House of Delegates:

"WHEREAS, At this time 75% of the care of children is in the hands of the general practitioner, and

"WHEREAS, About one third of the work of the general practitioner is in the field of pediatrics, and

"WHEREAS, It is believed that a separate examination in Pediatrics would stimulate the students and interns to inform themselves on matters of child care; therefore be it

"Resolved, That the House of Delegates of the American Medical Association hopes that the various state medical societies will use their influence to urge the various state boards of medical licensure to include a separate examination in Pediatrics in the requirements for medical licensure. It is suggested that the questions for such an examination be framed by, or with the help of, a practicing pediatrician."

The third subject discussed at this meeting was the possibility of setting up a long range plan for improved hospital training in pediatrics. Dr. Martin said that any such plan would have to come through or from the Council on Medical Education. However, any such suggestion could be sent to the Liaison Committee and be transmitted to the Council on Medical Education.

Recommendations: The committee feels that there is widespread misunderstanding of the relationship between the two societies. In order to help correct this we recommend that copies of the resolution passed by the House of Delegates, endorsing the programs advocated by pediatric groups, be sent first to every State Chairman of the Academy and then to each of the members of the Academy of Pediatrics.

We would like permission to ask Dr. Martin to see if the same resolution could be sent to each state medical society with a letter explaining the importance of cooperation of the two organizations.

I would like to express my appreciation of the important work of Dr. Crawford and Dr. Stringfield in contacting Dr. Martin and getting this underway when I was unable to be present in person; also of Dr. Martin's effective and courteous cooperation.

Respectfully submitted,

PHILIP S. BARBA, *Chairman*

It was moved, seconded, and carried that this report be accepted with thanks.

The following letter from the Board of Trustees of the National Society for Crippled Children and Adults was read by Dr. Munns, and the Secretary was authorized to send this out in mimeograph form to the members of the Academy:

"The Board of Trustees of the National Society for Crippled Children and Adults has recognized that research is an essential part of its program of services for the handicapped, combining with direct services and facilities and education of the public, of professional personnel and of the handicapped themselves, to make a three-pronged attack on the problem.

"Although a number of the state member societies are now carrying on minor research projects, it is the feeling of the Board of Trustees that these activities should be coordinated and expanded into a national program. At its meeting in Chicago last November, the Board instructed the Executive Committee by formal resolution to take active steps to initiate a program of research.

"The Executive Committee, in accordance with the instructions of the Board, is now making a preliminary investigation of the needs for research in the field of services for the handicapped and the projects which might be feasible for the society to undertake. In connection with this activity, a preliminary meeting was held with a representative of the National Research Council, looking toward possible use of that agency's services in the development of the research program of the National Society.

"As a further step in its preliminary investigation, the Research Committee has asked that I write you, as Liaison Officer from the American Academy of Pediatrics to the National Society, and to others serving in similar capacities, to secure from you any suggestions which you or the members of the Academy may have as to the general areas in which research relating to handicapping conditions may be needed and also of specific projects which you may wish to call to our attention. If, in your judgement, any of the suggestions you make should have priority over any other, would you please so indicate. Any suggestions which you or your colleagues may be able to make to the Research Committee will be very much appreciated.

"I hope that I may hear from you in the near future as our Research Committee wishes to proceed with its work as rapidy as possible and wishes to have the value of your comments and suggestions."

It was moved, seconded and carried that Dr. Munns be requested to compose a letter formulating the request of the National Society for Crippled Children and Adults to be sent to the members of the Academy.

Saturday Morning Session, June 25

The Saturday morning session convened at 9:20 a.m., June 25. An additional member, Dr. Borden S. Veeder, Chairman of the Reorganization Committee, was in attendance.

The session Saturday morning and most of the afternoon was devoted exclusively to the report of the Reorganization Committee. Dr. Veeder presented the report of the Committee and this was discussed in detail by the members of the Executive Board.

Dr. Veeder was instructed to take into consideration the views expressed at the Executive Board meeting by the members, to incorporate them in the recommendations of the Committee and to resubmit the whole thing to the Committee first, after which it was to be distributed to the Executive Board and to the State Chairmen.

The afternoon session convened at 1:50 p.m.

After further consideration of the report of the Reorganization Committee, the following reports were taken up: (Dr. Veeder retired and Dr. Hugh McCulloch, Dr. John Hubbard and Mrs. Elizabeth Lammie came in.)

EDITORIAL BOARD

"The office of the Editor-in-Chief of PEDIATRICS was moved on Dec. 31, 1948, from St. Louis to Chicago and is now housed at La Rabida Sanitarium in Jackson Park. This change resulted from the change made by the Editor-in-Chief in assuming new duties as Chief-of-Staff of La Rabida Sanitarium and Medical Director of the Council on Rheumatic Fever of the Chicago Heart Association. Processing the January, February and March issues of PEDIATRICS was already under way in the St. Louis office when the move was made, and was completed through that office. The April issue was started in the Chicago office and henceforth all issues will be from Chicago. Certain changes in personnel of office staff were made quickly and satisfactorily and there has been no disturbance in production. The new location has numerous advantages, both the satisfactory housing at La Rabida Sanitarium and the nearness to the Academy offices, the Chicago office of the George Banta Publishing Company of Menasha, Wis., and the more convenient nearness to Charles C Thomas, Publisher, in Springfield, Ill. The new location should be generally more convenient and more satisfactory.

"PEDIATRICS has prospered in this last six months covered by this report. Both the quantity and the quality of manuscripts submitted for publication have increased considerably. The Editorial Board is now able to select manuscripts carefully and critically, keeping in mind the high ideals set for publication and the place PEDIATRICS occupies in the activities of the Academy. The patient, careful and thoughtful consideration given to each manuscript by the several members of the Board assures to PEDIATRICS that these high ideals will be adhered to. Members of the Board who serve the Academy so well and without pay deserve and should receive the great appreciation of the Academy.

"PEDIATRICS has prospered, too, financially because together with the increasing cost of production there has been a greater increase in income from new subscribers, advertisers and general support from many sources. This has been accomplished during the time when income could have been decreasing due to general economic and business trends. The first year of operation showed a surplus of income over expenses. The publishers have used every means to bring this about. Certain changes in the format of PEDIATRICS will be made as soon as income justifies the slight increase in expense that would be incurred. Constant effort is made to improve format. The Editorial Board is fully conscious of the fact that the success of the publication will depend largely on the quality of manuscripts published and the position PEDIATRICS obtains in the field of medical writing. And, indirectly, this will influence the quantity and quality of advertising submitted and accepted for publication."

Dr. McCulloch reported the resignation of Dr. Leona Baumgartner as a member of the Editorial Board. No recommendations for her successor as yet had been decided upon.

The scope of the Section "The Pediatrician and the Public" edited by Dr. Paul Harper was discussed as well as the Section "TRENDS" edited by Dr. Hubbard.

It was moved, seconded and carried that the names of Dr. Herbert C. Miller, Dr. L. Emmett Holt, Jr., and Dr. Ralph V. Platou be accepted by the Board as members of the Editorial Board at the recommendation of the Editorial Board.

Dr. McCulloch was given a vote of sincere thanks for his editorial work with PEDIATRICS, and it was moved, seconded and carried that the report of the Editorial Board be accepted.

The Secretary was instructed to write a letter of acceptance of Dr. Park's resignation and thanks for this past service.

The C.P.A.'s accounting of the finances of the Study Committee was presented by Dr. Hubbard and left to a committee of three, consisting of Drs. Martmer, Bost and Stringfield, to be examined and reported at the Sunday morning session.

The report of the Committee on Allergy was presented and the Secretary was empowered to find out more definitely about the conditions surrounding the proposed primer.

COMMITTEE ON ALLERGY

The Section on Allergy met on Nov. 20, 1948, at Haddon Hall, Atlantic City, N.J.

A proposal by Dr. Stanley Freedman, Providence, R.I., to form a national group to aid in the care of allergic children was discussed. This was considered to be too large a job for the Academy.

The question of writing a primer in pediatric allergy similar to that produced by Dr. John A. Toomey was discussed. Dr. Deamer stated that it might be well to write pamphlets concerning one phase of the subject at a time. Dr. Hill suggested that this might be done, perhaps, with hay fever, or, more practically, with an outline of the method of treating an acute attack of asthma. Other topics might be on environmental control, skin testing and diet. It was suggested that a primer on the treatment of the acute attack of asthma and the environment control of asthma be of value to start with.

It was suggested that Dr. Ratner take steps to find out what type of examination is given for subcertification in pediatric allergy. The impression was that these examinations are merely more formalities than anything else. Dr. Hill felt that really stiff examinations should be given. Dr. Ratner discussed this matter, later, with Dr. Lee Forrest Hill who suggested that it be taken up with Dr. Schloss and Dr. Robert E. Cooke. After discussion with Dr. Schloss and Dr. Cooke in New York, Dr. Ratner was told that they had no objection to the examinations being taken over by the Committee on Allergy.

The question of where to publish papers on pediatric allergy was discussed. It was the opinion of those present that these should be published, so far as possible, in pediatric journals.

It was decided at this meeting that further exploration of the question of examinations in the subspecialty of allergy be considered by the Pediatric Certification Allergists, and the question of the primer on the management of acute attack of asthma was thought advisable.

Respectfully submitted,

BRET RATNER, *Chairman*

SECTION ON SURGERY

The primary reason for the formation and development of the Section on Surgery is to assist in promoting objectives of the Academy as set forth in Article III of the Constitution. To this end the aims of this Section are:

1. To provide a forum for the initiation, discussion and development of ideas and problems related to the surgery of infants and children.
2. To stimulate the study and teaching of the surgery of infants and children.
3. To disseminate the principles of children's surgery through Academy channels to the medical profession generally for the purpose of providing better surgery for children everywhere.
4. To bring into the Academy those surgeons whose work is entirely, or to a high degree, devoted to infants and children.
5. To assist the Program Committee or any other appropriate committee in the general educational program for the membership of the Academy.

There should be the closest cooperation with the program committee to assist it in presentation of subjects which may have a surgical aspect. It is suggested also that members of the Surgical Section be placed individually on as many committees as possible in order that they may become more familiar with the activities of the Academy and also for the broadening educational value to the surgical members themselves.

The following suggestions for participation in programs are presented:

A. Before the general assembly:
   1. Presentation of surgical aspects of appropriate subjects either in the body of a symposium or a paper immediately following one which has surgical implications.
   2. Surgical treatment of common conditions, avoiding technical details.
   3. Discussions of preoperative and postoperative care.
   4. Discussions of postoperative complications.
   5. Panel discussions on controversial subjects.
   6. Presentation of research problems related to surgical conditions in children.
   7. Reports of recent advances in surgical pediatrics.

B. Before small groups: Round table discussions of specific surgical conditions.

C. Before the Surgical Section itself—which meetings shall be open to the general membership:
   1. Discussions of technical problems and technic.
   2. Discussions of progress of research.
   3. Discussion relating to education in pediatric surgery.
   4. Discussion of the activities and problems of the section.

The planning committee of the section is as follows: Dr. O. S. Wyatt and the chairman for a three year term; Dr. Jesús Lozoya Solís and Dr. Robert E. Gross for a two year term; Dr. William E. Ladd and Dr. Henry Swan, Jr., for a one year term.

Respectfully submitted,

HERBERT E. COE, *Chairman*

The president read a letter from Dr. Shaffer, Chairman of the Committee on School Health, explaining that he thought it was best not to make recommendations until Congress had acted upon the School Health Bill.

After the action of Congress, the Secretary was authorized to send out a statement on the part of the School Health Committee.

COMMITTEE ON TUMOR REGISTRY

A conference of the Committee members in New York City was held May 20, 1949.
The following cases have been added to the Registry since the report of October 1, 1948:

Hyperplasia of right axillary node	6 yrs.
Neuroblastoma	5 yrs.
Neuroblastoma	28 mos.
Neuroblastoma	17 mos.
Neuroblastoma	3 yrs.
Cavernous hemangioma	3½ yrs.
Hypertrophic angioma	15 mos.
Hemangioma hypertrophicum	4 mos.
Juvenile naevus	4 yrs.
Lymphangioma	4 yrs.
Osteogenic sarcoma	11 yrs.
Bone angioma	11 yrs.
Eosinophilic granuloma	3 mos.
Wilms' tumor	5½ yrs.
Wilms' tumor	20 mos.
"Tumor" of Thymuskopf	3 yrs.
Complex tridermal teratoma	7 wks.
Ganglioneuroma	14 yrs.
Herniated brain tissue (bridge of nose)	5 mos.
Complex teratoid hepatoma	20 mos.
Retinoblastoma	9 yrs.
Teratoma, embryonal	17 wks.
Mixed neurogenic tumor	9 mos.
Hematomegaly, etiology unknown	3 mos.

EDUCATION

An exhibit entitled, "Control of Cancer in Childhood" has been completed. This is the fourth exhibit prepared since 1946, all of which are available without charge for educational purposes. It was shown at the annual convention of the New Jersey State Medical Society. It will be used at the annual convention of the American Medical Association in June 1949, and the annual convention of the American Academy of Pediatrics in November 1949. Another exhibit was used at the Minnesota State Medical Society Convention, May 9, 10 and 11, 1949.

Data from the Registry has been or will be used in 1949 for teaching purposes—graduate and undergraduate—in New York, New Jersey, Michigan, District of Columbia, California and Hawaii.

PAMPHLET: CANCER AMONG CHILDREN

Through the courtesy of Dr. George M. Wheatley a pamphlet entitled, "Cancer among Children," a report which appeared in the January issue of the Statistical Bulletin of the Metropolitan Life Insurance Company, was distributed to all the members of the American Academy of Pediatrics.

PROPOSED REGISTRY OF JUVENILE PATHOLOGY

The Chairman of the Committee visited General Dart and Colonel J. E. Ash of the Army Institute of Pathology in Washington, D.C., April 6, 1949, and considered that the discussion held that morning had advanced the situation as far as could be expected up to that date.

A questionnaire concerning the proposed Registry of Juvenile Pathology was submitted to the heads of the pediatric departments of all medical schools in the United States.

Thirty-two of the 79 replied. A survey of the members and consultants of this Committee was also made. Replies were received from 5 members and 9 consultants.

Pediatric Department Heads
Replies received 32

	For	Against
	28	4
Under jurisdiction of American Registry of Pathology	18	
Under other jurisdiction	10	

Children's Tumor Registry Committee
Replies received 14

Members		Consultants	
For	Against	For	Against
2	3	7	2

3 voted "yes" with reservations.
2 voted "no" with reservations.

SUMMARY: Total Replies 46
Favoring establishment of a Registry of Juvenile Pathology 37
Favoring establishment of a Registry of Juvenile Pathology under the American Registry of Pathology 18
Against establishment of a Registry of Juvenile Pathology 9
Against establishment of a Registry of Juvenile Pathology under the American Registry of Pathology 10
Further replies are expected. Your Committee will defer any recommendation for action on this proposal until our next report.

SPECIAL COMMITTEE FOR THE STUDY OF RADIATION EFFECTS IN CHILDHOOD

This Committee held a meeting March 31, 1949. A copy of the minutes is attached.

Respectfully submitted,

HAROLD W. DARGEON, *Chairman*

In addition to the report on the Committee on Tumor Registry, the following recommendation was submitted:

"Grant-in-aid: The Children's Tumor Registry has been supported up to the present by private grants. The accomplishment of a significant part of the program has been realized only through a considerable amount of volunteer assistance. Your Committee believes extension of the three activities of the Registry, namely, diagnosis, education, and registration of cases, should continue. Dependence upon such volunteer aid will still be necessary, but support by a grant-in-aid would permit further developments of the program which are impossible without such assistance.

"Recommendation: It is recommended that the Executive Board endorse an application of the Children's Tumor Registry to the Babe Ruth Foundation for a grant-in-aid and that the Secretary communicate with Mr. John H. Teeter of the American Cancer Society, 47 Beaver St., New York 4, N.Y., the organization administering that fund, affirming this endorsement."

The Secretary was empowered to write to Mr. Teeter of the Babe Ruth Foundation and tell him that the Children's Tumor Registry in applying for funds has our interest in that we have an active committee in the Academy, headed by Dr. Dargeon, and working at the Children's Tumor Registry, and we would appreciate his giving favorable consideration and attention to their requests.

Dr. Grover F. Powers' resignation from the ICH Committee was accepted with regret.

A Committee consisting of Dr. Hoyer and Dr. Beaven was appointed to bring in recommendations for someone to fill out the unexpired term of Dr. Powers on the ICH Committee.

(Recess)

The Executive Board carried on a rather lengthy discussion on the question of publicity and public relations and how they should be conducted. Some remarks of Mr. Hiller's were read and the success of the pamphet, "The Road Ahead. . ." was commented upon.

Following is Dr. Barba's report:

COMMITTEE ON PUBLICITY AND PUBLIC RELATIONS

There is very little to report since the meeting of the Board in Atlanta. Dr. Stringfield of this committee was active at the AMA meeting. As reported by the Liaison Committee, he filled in the gap of my absence and worked with Dr. Crawford and Dr. Martin to smooth the disturbed relationship between the AMA House of Delegates and the American Academy.

This committee still feels that there should be a decided increase in the effort to improve the public relations angles in the membership at large. This cannot be done by mailing large quantities of material which is not read.

The State Chairmen should be utilized to a greater degree and should be kept informed on all developments of policy and all the work of the various committees.

Personal contact with the membership would be the ideal set-up. A full time man with travel expenses would do a big job of unifying the opinions, the knowledge, and the reactions of the membership.

Failing this we should use short, dynamic letters sent to the Chairmen and from them to the members.

There should also be brief but informative letters or editorials in PEDIATRICS, preferably placed strategically in the scientific part of the journal.

So far as a full time Publicity and Public Relations man is concerned, we feel that such a place could be properly filled only by a physician. At present we do not feel that the use of part time Public Relations Counsel would be either economical or effective.

Respectfully submitted,

PHILIP S. BARBA, *Chairman*

COMMITTEE ON LEGISLATION

The American Academy of Pediatrics, which I have the honor to represent as Chairman of its Committee on Legislation, by action of its Executive Board on April 16, 1949, disapproved the passage of S. 5 and bills of similar purpose, such as S. 1679, now under your consideration.

Regarding S. 1679, the National Health Insurance and Public Health Act, we have never before studied a bill presented to the Congress the preamble of which has contained so many misstatements, inaccuracies, and observations at variance with the truth, evidently for purposes of propaganda, as are contained in Sec. 2 under the caption "Declaration of Purpose."

Seven "conditions" are named in Sec. 2, a few of which must be admitted to exist, based largely upon geographic and economic situations, which the bill attributes solely to one factor, namely, "our archaic system of paying for medical care."

For purposes of clarity, let us for the moment rearrange (but not change) the phraseology of the paragraph in Sec. 2 beginning on line 7, page 5, and ending in line 2 on page 6, to wit: The following conditions (numbering seven) have resulted from OUR ARCHAIC SYSTEM OF PAYING FOR MEDICAL CARE based on public and private charity for the poor, on unpredictable and often unbearable costs to the otherwise self-supporting, and on disproportionate charges for the well-to-do.

Who but the adherents of socialized medicine and those who see in the bill free medical care (but will not receive it) can charge as "archaic" a system of paying for medical care which is and always will be a basic economic law for the purchase of personal services in accordance with the principle that the laborer is worthy of his hire? Surely, the vocal labor leaders propagandizing this measure would be the last to deny this principle as it applies to the workers they represent!

Webster defines the adjective archaic as "pertaining to an ancient time, custom or relic."

Those who designate the present system of paying for medical care as archaic, although a better definition would be "time-honored," might peruse Webster a bit further and find adjoining the definition of archaic another word arising from the same stem, which many of these propagandists, from their vociferous utterings, would like to apply to physicians distributing medical care. That word is "archaeopteryx," defined by Webster as a "fossil bird of the Jurassic age, having teeth, vertebrae in its tail, and claws on its wings, being a link between birds and reptiles." Is it possible that our patients, many of whom have been our loyal adherents through the years, would regard us

as a flock of vampires or the vicious hybrids known as archaeopteryx? If so, why do they still employ us, usually with grateful appreciation for medical services rendered? "Archaic" had better be eliminated from Sec. 2.

Let us for a moment examine the seven "conditions" ascribed to the so-called archaic system of paying for medical care.

Condition 1, Sec. 2, page 6, line 3, quote: "The inability of the VAST MAJORITY of our people to meet the shattering cost of serious or chronic illness." This statement is entirely out of keeping with the truth. The majority of our people have been able to meet the costs of illness, however shattering, or have had medical services provided for them under the so-called archaic system.

Sampling of our population by well conducted polls has shown decidedly that the majority of our people do not wish a change in the present method of payment for medical care, nor can it be denied that the present and time-tested system of paying for medical care has failed to contribute its share "of our Nation's strength, productivity, and wealth," to quote from the second paragraph of Sec. 2.

Condition No. 2: "The inability of most of our people to benefit from modern preventive medicine." This statement is an absolute falsification of fact, of which I may speak with the authority of a pediatrician in practice among children for over two score years. As the twig is bent, so the tree will grow. Pediatricians are those who control the growing human plants, who form a special group of physicians devoting two thirds to three quarters of their time to preventive medicine and who, with the aid of the general practitioners embracing their methods, contribute most largely to the practice of preventive medicine.

The increase of over a score of years of the span of life has been due largely to preventive medicine as applied to infants, children and adolescents, so that it may no longer be said that "the good die young," for good preventive medical care has enormously reduced the morbidity and mortality among the young in all categories save one, injuries and deaths from accidents, these resulting from the tensions and perils of the machine age and not from any lack of preventive medicine.

Condition No. 3: "A critical shortage of physicians, dentists, hospital administrators, dental hygienists, nurses, sanitary engineers and other health personnel." This is admittedly true in part, but will the institution of compulsory health insurance increase or decrease the attraction of medicine and allied professions as careers for prospective students? The obvious answer is that it will decrease and act as a deterrent to the enlistment of physicians in the profession of medicine.

Condition No. 5: "Wholly inadequate provision for the health needs of our farm families and agricultural workers." These groups through the acquisition of good roads and modern transportation are within a few hours' reach of facilities for the most modern medical and surgical treatment, as well as sharing in the benefits of nearby facilities now being extended to rural areas through the Hill-Burton Act and other legislative acts of the Congress.

The same statement applies to condition No. 7, relating to maldistribution of both personnel and facilities. One might justly criticize the wording of this condition which contains the phrase—"others (areas) which suffer an almost total lack of decent medical care!" If not decent, these areas must have only indecent medical care; the bill might have been drawn with more attention to the choice of truly descriptive adjectives.

Also, in condition No. 7, occurs the paragraph—"Because prolonged failure effectively to relieve these shortages and to correct this maldistribution will result, inevitably, in the further extension of medical care directly by government agencies." Is this a threat or a delusion? The same question may be pertinent to the next paragraph threatening a "system of state medicine, paid for from tax funds and rendered by regimented doctors." Is this a *post hoc, ergo propter hoc* and may we ask in the words of Lo, the Poor Indian (who has never received "decent" medical care under the auspicies of governmental medicine), How! How! is it going to work out that way?

We would like to rearrange, but not change, the wording of Sec. 2 (G), in the interest of clarity, line 23, page 8, to line 2, page 9, to wit: "By establishing a system of Prepaid Personal Health Insurance on the principles of Social Insurance, to provide a sound economic foundation for OUR FREE SYSTEM OF MEDICINE, and to correct the maldistribution of health personnel and facilities."

The bill thus obligates the measure in establishing a FREE SYSTEM OF MEDICINE, but in the

next breath on the opposite page, Sec. 3, page 9, line 3, retracts the promised bait of a free system of medicine by a diametrically opposite promulgation actually providing for the degrading, obnoxious, horrid (sic) "means test," as follows: "In establishing a system of National Health Insurance, it is the policy of this Act that those persons and their dependents who are insured under the provisions of the Act shall PAY FOR ITS BENEFITS IN PROPORTION TO THEIR INCOMES, and shall, therefore, receive its benefits as a right and not as charity." A "means test," for universal economic law under which we all live, pay our income taxes, purchase our food, clothing and shelter, rears its ominous head again on page 74, line 3, Sec. 422, (b), to quote: "If regular payments from its members are required for purposes of financing the cost of providing the medical care and the maintenance and operation of the cooperative (Farmer's Experimental Health Cooperatives) and are graduated in relation to INCOME OR INCOME GROUPS."

But in Title VI, in which we as pediatricians are especially interested, relating to maternal and child care, appears the prohibition in regard to acceptance of a State plan, page 96, lines 13, 14 and 15, that such plan shall (6) "provide that determinations as to the children to be furnished services under the plan shall be made WITHOUT REGARD TO ECONOMIC STATUS."

The American Academy of Pediatrics has repeatedly protested against this principle of free treatment for all individuals by the Federal and State Governments in the following language:

The American Academy of Pediatrics, regarding the provisions for maternal and child welfare (referring to the National Health Act of 1939, S. 5, S. 1679 and similar bills of the 81st Congress) favors the use of public funds to provide such services TO THOSE GROUPS OF THE POPULATION UNABLE TO PAY FOR MEDICAL SERVICES, to the end that the standards of medical care may be maintained at a high level among such groups.

The Academy of Pediatrics does not favor the use of Federal funds for those ABLE TO PROVIDE GOOD MEDICAL CARE FROM THEIR OWN RESOURCES.

The American Academy of Pediatrics again opposes the passage of legislation which violates the principles set forth above and registers its protest against the adoption by the Congress of S. 1679 as at present written.

In conclusion, let me again refer to Sec. 3, page 9, lines 4 to 8, to wit: "Those persons and their dependents who are insured under the provisions of the Act shall pay for its benefits in proportion to their incomes, and shall, therefore, receive its benefits as a right and not as charity."

The insinuations and aspersions implied in this paragraph and cast upon charity associated with the bestowal of medical care by physicians, we resent in no uncertain terms. Since when has charity been condemned and decried as an attribute of humanity?

From the time of Scriptual writings, charity has ever been looked upon as one of the humanities worthy of praise and not of censure. Indeed, Holy Writ tells us in I. Corinthians that—"charity suffereth long and is kind; charity envieth not; charity vaunteth not itself, is not puffed up, rejoiceth not in iniquity, but rejoiceth in the truth; and now abideth faith, hope, charity, these three; but the greatest of these is charity."

A recent report (*Medical Economics,* March, 1949, page 73), based on the Sixth Medical Economics Survey, of the time given to charity by physicians, states that:

"Six hours a week were donated to charity patients by the average independent physician in 1947.

"This was equal to about 10% of the practitioner's total working hours.

"Among all independent physicians in 1947, the total donation exceeded 36 million charity hours.

"The dollar value of those donated hours was more than 135 million.

"Eighty-eight per cent of all independent physicians attend charity patients to some extent.

"Can any member of any profession in this audience within the reach of our voice challenge this record, or even match or exceed this time of service to humanity which is rendered by physicians?"

Respectfully submitted,

JOSEPH S. WALL, *Chairman*

Requests for the annual meetings were discussed, both as to where they should be held and when. It is a general opinion that, where possible, the meetings be held in October and that the Secretary be asked to give careful consideration to the question of having the place of all future meetings in Chicago. This question had been raised previously and had received general approbation. Dr. Grulee

called attention to the fact that the annual meeting in 1950 would be held in Chicago at the Palmer House; that the meeting of 1951 would probably go to Toronto, but that the Boston meeting, which would come in 1952 and had already been projected, would probably have to be changed as to locality because of the lack of proper hotel accommodations in that city.

The following resolution by Dr. Hurtado was read and approved.

"Whereas, District IX is so constituted that all different Latin American countries, some of them as far as Chile and Argentina, do not permit the frequent reunion of all the members of this District, and

"Whereas, The Pan-American Pediatric Congress is the best and perhaps the only opportunity for the Latin American members of the Academy to get together; it would be wise and desirable to take this opportunity to celebrate a general assembly of District IX, and therefore have its business meeting to elect the Chairmen."

The Sunday morning session, June 26, convened at 9:10 a.m., President Sisson presiding. Dr. Hubbard and Mrs. Lammie joined the group.

The report of the committee which had been named to look over the report of the Survey finances presented the following:

"The reports of the accountants and the financial records have been reviewed and we recommend that we accept the report as it is and that a copy of each record be sent to each of the contributors."

After discussion of the recommendations, it was moved, seconded and carried that the tangible assets of the Study Committee be given to the ICH Committee as part payment of funds advanced by them and that the Study Committee be dissolved.

The original report of the Committee was accepted.

Dr. James L. Wilson came at this time to discuss the question of the ICH Committee and its doings. The first question concerned Dr. Powers' resignation. This was accepted with regret and it was moved, seconded and carried that Dr. Albert Kaiser be requested to accept the appointment to fill the unexpired term of Dr. Powers.

Dr. Wilson then discussed the report of the ICH Committee which had been placed in the hands of the Executive Board previous to the meeting. The question of how the ICH Committee should proceed and what phases of the work should be stressed were discussed in detail.

It was moved, seconded and carried that, if possible, the results of the Study, when published, should appear in "TRENDS" in PEDIATRICS.

The Chairman of the ICH Committee was directed to have an interpretative report with recommendations in the hands of the Board by the time of the Executive Board meeting in November.

It was moved, seconded and carried that the report of the ICH Committee be accepted.

There was a long discussion on the question of the financial situation so far as the ICH Committee was concerned.

It was moved, seconded and carried that a Committee of three be appointed by the President to work out a scheme, after having consulted Dr. Hubbard, by which the necessary functions for the fiscal year be carried on and make recommendations accordingly. The following committee was appointed: Dr. George Munns, Chairman; Dr. Crawford W. Bost; Dr. Philip S. Barba.

Dr. Glidden Brooks then reported on the work he is doing in Philadelphia since coming with the Academy.

After some discussion regarding the question of considering a man to take the place of Director of the society, the meeting was adjourned.